

The influence of movement speed on the ability to learn reaching movements in health and after stroke.

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I,..... (Ulrike Hammerbeck) confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Abstract:

Fast movements have traditionally been avoided during rehabilitation after stroke for fear that they might increase spasticity. However movements in daily life require alterations in speed. In healthy individuals (n=14), 1 week of intensive reaching training in a robotic manipulandum biased participants movement speed during other tasks performed in the manipulandum: people who trained to move slowly tended to move more slowly whereas the opposite was true for the fast training group. Yet the improvement in movement accuracy was the same in both groups.

In chronic stroke survivors (n=37) functional ability before training was determined by muscle stiffness and weakness. Endpoint accuracy improved after training at both movement speeds in all participants apart from those with the greatest sensory impairment. However, training at the different speeds modified different kinematic parameters of the task (e.g. movement trajectory versus velocity profile) so that training at one speed did not generalise well to movements performed at non-trained speed. Most interestingly muscle stiffness was not increased by training at high velocity. Unexpectedly, it was reduced and functional ability as well as the ability to reach outside of the robotic manipulandum improved.

Transcranial magnetic stimulation on a sample of these stroke participants (n=19) was used to test the hypothesis that ipsilateral drive to proximal muscles from the non-stroke hemisphere is important in determining recovery of arm and shoulder movement. MEPs could be elicited in at least 25% of muscles from both hemispheres but contrary to expectation, arm function was only correlated to the drive from the affected hemisphere, even in patients with the greatest impairment. Muscle activation patterns were not significantly different between the affected and unaffected limb and training did not alter these.

Training at a fast speed is not detrimental in patients after stroke and should be encouraged to increase the variety of movements patients can perform.

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Abbreviations

AC	Affected contralateral
AI	Affected ipsilateral
ANOVA	Analysis of variance
BDNF	Brain derived neurotrophic factor
CIMT	Constraint induced movement therapy
CST	Corticospinal tract
CT	Computerised tomography
DOF	Degrees of freedom
EMG	Electromyography
LI	Laterality Index
LTD	Long term depression
LTP	Long-term potentiation
M1	Primary motor cortex
MAS	Modified Ashworth Scale
MEP	Motor evoked potential
MN	Motor neuron
MRC	Medical Research Council
MRI	Magneto-resonance imagery
MSO	Maximal stimulator output
n	number
RST	Reticulospinal tract
SAT	Speed-accuracy trade-off
SD	Standard deviation
SE	Standard error
TENS	Transcutaneous electrical nerve stimulation
TMS	Transcranial magnetic stimulation
UC	Unaffected contralateral
UI	Unaffected ipsilateral
UMN	Upper motor neuron

Publications in relation to this thesis

Hammerbeck U, Yousif N, Greenwood R, Rothwell JC , Diedrichsen J. Movement speed is biased by prior experience. *J Neurophysiol* 2014; 111(1): 128-133

The results from this paper are described in Chapter 4.

1. Introduction

1.1. Introduction

During daily activities movements are performed at a wide variety of movement velocities dependent on the movement goal, i.e. reaching to stop a child from stepping onto a road or reaching to insert a key into a lock. However, our knowledge of how movement speed affects motor learning in health and after stroke is limited (Francis, 2008, DeJong et al., 2011, Shmuelof et al., 2012). Current evidence –based intervention protocols, e.g. Constraint-induced Movement therapy (CIMT)(Liepert et al., 2000) as well as clinical guidelines for stroke rehabilitation (Royal-College-of-Physicians, 2013) do not incorporate movements at various speeds, nor emphasise the need to move at a variety of movement speeds. Although movement speed variation is probably incorporated into a range of therapeutic activities when treating the less affected individual, this probably doesn't occur when treating patients with more severely affected upper limbs, which are not incorporated into functional activities (Lang et al., 2009). A hesitance to encourage fast movements in rehabilitation paradigms probably stems, at least partially, from the historical emphasis on promoting normal movement and preventing movements that would degrade movement quality (Bobath, 1990). Fast movements, it was thought, could increase spasticity, a velocity dependent muscle stiffness observed after stroke (Pandyan et al., 2005). After a neurological insult individuals tend to move slowly (Wagner et al., 2007, DeJong et al., 2011), and continual exposure to this same movement velocity is likely to reinforce their slowness of movement, through use-dependent learning mechanisms (Diedrichsen et al., 2010). However individuals affected by stroke (DeJong et al., 2011) as well as other neurological conditions (Mazzoni et al., 2007), are able to move faster than their preferred movement speed and studies have indicated that faster movements improve the quality of movements (van Vliet and Sheridan, 2007, DeJong et al., 2011).

Movement trajectories, for a multi-joint movement, like reaching are very stereotypical, but achieving these patterns with spatio-temporal variations requires complex neuromuscular computations (Soechting and Lacquaniti, 1981). Reduced ability to perform functional movements,

like reaching after stroke, is caused by a combination of impairments resulting from damage to the corticospinal pathway. Muscle weakness, sensory loss and spasticity all contribute to the impairments (Zackowski et al., 2004, Wagner et al., 2006). Intensive training after stroke can promote recovery, even in the chronic phase, by inducing improvements that result from recovered function of the affected effectors rather than compensatory strategies (Barker et al., 2008, Levin et al., 2009). However, task repetition and time spent training upper limb movements tend to be very low in clinical practice (Lang et al., 2009, Hayward and Brauer, 2014), as well as in many experimental designs, and is not comparable to the amount of training shown to be effective in evidence from animal models (Nudo et al., 1996). Training with such a high number of repetitions is however achievable in human stroke survivors (Birkenmeier et al., 2010) and using a robotic manipulandum which eliminates the effect of gravity does enable individuals with more severe weakness to perform sufficient repetitions of reaching movements to promote strengthening and recovery (Coscia et al., 2014).

1.2. Research Aims:

The aim of this thesis is to investigate how individuals affected by stroke can improve reaching accuracy with intensive training. Specifically, I investigate how training at slow and fast movement speed influences the habitual movement speed in healthy individuals. I further investigate how reaching performance is altered in health and in chronic stroke when training is performed at either slow or fast movement speed. In particular, the study was designed to recruit a more severely affected stroke population. It establishes whether training at fast movement speed after stroke is detrimental to motor recovery, and how the clinical impairments resulting from the stroke influence learning.

1.3. Research Question

- Does training at either fast or slow movement speed alter the habitual movement speed in healthy individuals?

- How does training at a specific movement speed influence learning and generalise to other movement speeds in health and after stroke?
- Does learning at slow movement speed rely on improving feedback integration, and learning at fast movement speed on improved update of the feed forward motor plan?
- How does the clinical presentation of stroke patients affect performance and learning?
- Can I observe improvements in clinical outcomes after this short training protocol, and does it differ between the training groups?
- Do ipsilateral pathways from the unaffected motor pathway contribute to proximal motor function and recovery in this more severely affected patient group?
- Can EMG activation patterns contribute to our understanding of which cortical pathways assist with motor function in chronic stroke patients?

1.4. Organisation of thesis

This thesis explores the influence of movement speed during training on motor relearning in health and after stroke in 4 chapters.

- 1.) **Chapter 4** explores the effect that training at a specific speed has on healthy individual's habitual movement speed.
- 2.) **Chapter 5** presents the learning data of stroke patients, and demonstrate a training speed specific learning effect that distinguishes between mechanisms in the two protocols. I further investigated the effect that impairment has on the performance of this task and how it influences motor learning.
- 3.) **Chapter 6** investigates the relationship of the ipsi-and contralateral hemispheric innervation, established by transcranial magnetic stimulation, on learning and how this is changed by training.
- 4.) **Chapter 7** expands on the neurophysiological investigation by studying EMG activation profiles of the affected and unaffected upper limb and the effect of training.

This thesis contributes to our understanding of the influence of movement speed during training regimes, in healthy individuals as well as in patients affected by stroke. It explores the effect that a set movement speed, during training, has on the performance of consecutive movements at

the trained and non-trained movement speed. I investigate if stroke patients can tolerate an intensive training programme and how the individual's clinical impairment influences performance and learning in this supported reaching task.

2. Background

2.1. Stroke

Stroke is the leading cause of physical impairment in the developed world impacting on individual's independence and the ability to fulfil life roles (WHO, 2001). Outcome after stroke is improving as a result of recent research addressing stroke prevention by lifestyle changes, reduced severity of early morbidity after stroke by hyperacute thrombolysis, and improved subsequent recovery using integrated interdisciplinary inpatient and early discharge care and therapy programmes (Veerbeek et al, 2014). However, with an ageing population the prevalence of age-associated diseases like stroke is likely to increase. As 40% of the 152 000, patients suffering a stroke every year in the UK never recover full upper limb function (Royal-College-of-Physicians, 2013) it is essential to strive to improve rehabilitation techniques to improve patients functional independence and outcome after stroke (Langhorne et al., 2011).

A stroke results from the loss of blood supply to the brain or a part thereof resulting in a lack of oxygenation and thereby damage to brain tissue. This interruption can be ischaemic or haemorrhagic. By the nature of the pathology, the insult can occur in any part of the brain, affect cortical or subcortical structures, and lesion size can vary greatly (Dobkin and Dorsch, 2013). If the lesion is located in the sensory-motor system it results in altered corticospinal connectivity and alterations in the formation of the cortical command, leading to difficulties in performing functional movement.

Problems with altered control of movements and actions and the implications these have on functioning have been divided by the World Health Organisation (WHO, 2001) into impairments at a body structure and function level, the limitations that these impairments impose on daily activities, and how they restrict participation in life roles. Although improvements in activity and participation are typically the true goals of rehabilitation, and can be used to measure recovery, these improvements can be achieved either by reducing impairments or by developing compensatory strategies to adapt to the impairments (Levin et al., 2009). This study focussed on changes in

impairment, measured the patients' symptoms and alterations due to interventions at an impairment level.

Common presentations after a stroke include contralateral weakness, reduced control of movement and poor coordination, difficulties with speech, including receptive and expressive dysphasia, sensory and visual disturbances, coordination difficulties, cognitive changes and fatigue (Langhorne et al., 2011).

2.2. Proximal upper limb symptoms

Disturbance of proximal upper limb control is as prevalent as distal difficulties with movement, however, it is frequently less of a priority in the limited available rehabilitation sessions, yet it is a source of continued disability and limitation of function that impacts on patient. Current evidence specifically supports CIMT (Liepert et al., 2000, Langhorne et al., 2014), an intervention for individuals with relatively mild distal impairment. These individuals have a good prognosis for at least some recovery of function (Prabhakaran et al., 2008). Therefore it was of particular interest to establish if it is possible to improve the effectiveness of intervention for the more severely affected population who present with proximal upper limb weakness and difficulties with reaching. Various trials have investigated stroke survivors performance for supported and unsupported reaching movement and the effectiveness of different training approaches (Barker et al., 2008, Birkenmeier et al., 2010, DeJong et al., 2011, Mehrholz et al., 2012, Duff et al., 2013, Patten et al., 2013, Subramanian et al., 2013, Milot et al., 2014). However, movement repetition has been low in many of these designs and the effect of altering the movement velocity in these reaching movements has not been systematically investigated.

Investigations of reaching describe kinematic alterations that include reductions in movement velocity (Wing et al., 1990, DeJong et al., 2011), changes in movement smoothness with increased number of sub-movements (Levin, 1996, Beer et al., 2000), reductions of reaching extent and thereby the available functional workspace (Wing et al., 1990, Kamper et al., 2002, Zackowski et

al., 2004, Beer et al., 2007, Ellis et al., 2011), and reduced individuation of shoulder and elbow muscle activity (Beer et al., 2000, Zackowski et al., 2004, Roh et al., 2013).

These abnormal movement patterns during reaching are due to a number of underlying impairments (Zackowski et al., 2004). It is now recognised that muscle weakness is a major contributor to movement difficulties but abnormal activation patterns, spasticity and sensation all influence functional ability (Zackowski et al., 2004, Ada et al., 2006, Wagner et al., 2006).

2.2.1. *Muscle weakness and dexterity*

Weakness is caused by a reduction or an interruption of descending corticospinal drive (Lawrence and Kuypers, 1968). This is due to neuronal cell death in the primary (M1) or secondary motor areas of cortex in cortical stroke, or due to damage of descending axons in the corticospinal tract (CST) in subcortical stroke (Lemon, 2008). These descending motor tracts do not only consist of the direct cortico-motoneuronal tracts, known to be important for primate dexterity but also a complex network of indirect corticospinal connections and corticobulbar connections, via the reticulospinal (RST) and rubrospinal tracts (Lawrence and Kuypers, 1968, Lemon, 2008). Insufficient activation of the motoneurons (MN) results in weak or absent muscle contractions. With time, the reduced descending signals lead to alterations in motor unit recruitment, firing patterns, muscle fibre type, muscle length and length-tension relationships and results in disuse atrophy in stroke patients (Ramsay et al., 2011).

The innervation of distal finger musculature differs from proximal muscles in that there is greater reliance on CST and direct connections to the ventral horn, resulting in severe weakness after damage of this pathway as established in animal models (Lawrence and Kuypers, 1968, Lemon, 2008). Proximal and axial muscles have however, additional innervation from the uncrossed ipsilateral CST and bilateral reticulospinal tracts (Lemon, 2008), with widely divergent innervations across multiple spinal levels even spanning the cervical and lumbar region in monkeys (Matsuyama et al., 1999). This structural arrangement means that proximal limb muscles as well as trunk muscle

preserve a greater amount of muscle strength after single lesions (Zaaimi et al., 2012). This animal study demonstrated increased prevalence of reticulospinal responses when stimulating the medial longitudinal fasciculus after discrete lesions in monkeys. Interestingly, the extensor muscles were not innervated by these pathways. Extensor weakness is a very common presentation after a stroke and this finding might reflect the importance of the CST input to extensor muscles.

2.2.2. *Spasticity/Abnormal muscle tone*

Another common presentation after stroke is an alteration of muscle tone, called spasticity. Spasticity has been defined as: 'disordered sensorimotor control resulting from an upper motor neuron lesion, presenting as intermittent or sustained involuntary activation of muscles' (Pandyan et al., 2005). Spasticity is not evident immediately after a stroke but evolves over the initial 3 months (Dietz and Sinkjaer, 2012). This gradual evolution of altered muscle activity is thought to be due to a number of factors, namely 1) changes in the afferent input to spinal MN, 2) changes in reflex circuits affecting MN excitability, and 3) changes in the intrinsic properties of the MN (Brown, 1994). Because of altered muscle activation patterns, disuse and maintained posturing, the muscle properties change over time and contribute further to reduced control of movement (Graham, 2013). The interplay between the altered neural drive and the changes in muscle properties make this a very difficult symptom to treat. Poor management can lead to the formation of contractures and resultant difficulties with motor control.

Although spasticity has traditionally been a major target for rehabilitation, the extent to which an enhancement in stretch evoked activity, i.e. spasticity, impairs functional movements is now being questioned (Malhotra et al., 2009). It is now thought that weakness after a neurological insult has a greater influence on disability than spasticity (Ada et al., 2006, Sorinola et al., 2009, Burke et al., 2013), and also that spasticity is not the cause of poor isolation of joint movements (Zackowski et al., 2004).

Because of the velocity dependence of spasticity, fast movements have traditionally been dissuaded (Bobath, 1979) , this might be one reason why the importance of alterations in movement speed of proximal upper limb training has not been mechanistically investigated. In clinical practice altered movement tone is assessed during rest or passive movement with the modified Ashworth Scale (MAS). This scale does however not specifically quantify spasticity but is rather a measure of hypertonus which includes neural as well as non-neuronal aspects of increased stiffness observed after neurological insult (Malhotra et al., 2009). A further limitation of this measurement techniques is that hypertonus is assessed at rest. However, the increased neural firing observed during rest is not evident during movement. During movement, spasticity causes a reduced ability to alter or modulate firing as the task requirements change (Mottram et al., 2009, Mottram et al., 2014). The functional limitations of spasticity are however of course evident during movement.

2.2.3. Sensory and proprioceptive feedback

The importance of sensory feedback to the control of movement is well recognised (Todorov and Jordan, 2002, Schmidt and Lee, 2011) and has been demonstrated in animal models (Asanuma and Arissian, 1984) as well as in humans (Rothwell et al., 1982, Jeannerod et al., 1984, Colebatch et al., 1990). Sensory feedback is reliant on a number of different inputs to the cortex with widely distributed peripheral sensory organs and spino-cortical pathways. Information of light touch, heat, vibration and joint position are relayed to the central nervous system and after stroke any of these senses can be affected depending on the site of the lesion (Schmidt and Lee, 2011). In the absence or with disturbed sensory feedback, i.e. in stroke involving the sensory system, recovery is reduced (Vidoni and Boyd, 2009) and slower (Chester and McLaren, 1989). This is more pronounced in the upper limb, probably due to greater task complexity. Sensory disturbance in stroke patients is a predictor of poor motor recovery (Kwakkel et al., 1996) and it compounds the effect of other symptoms due to stroke, i.e. reduced upper limb function due to muscle weakness (Stern et al.,

1971). The reduced feedback of limb position, due to sensory loss can also result in sensory neglect and reinforce the disuse of an upper limb with normal muscle power.

2.2.4. *Altered motor control*

Additionally to weakness, spasticity and sensory disturbance, stroke patients also present with difficulties in movement control. Movement stability is disrupted and muscle activation patterns are altered. Stereotypical arm movements emerge known as synergies (Twitchell, 1951) with co-activation of elbow flexion and shoulder abduction (Beer et al., 2000). This abnormal coupling of shoulder and elbow movement has been found to be a major contributor to abnormalities in reaching movements (Beer et al., 2000, Dewald et al., 2001, Zackowski et al., 2004). The flexion synergy is exacerbated by gravitational forces as well as increased task demand. Increased effort in activation of the affected upper limb (Prange et al., 2010) or distant effectors; i.e. example walking, also increase the synergistic activation.

In clinical practice, synergies were historically seen as an indicator that the task was too difficult and treatment intensity was matched not to elicit them (Bobath, 1979). Stroke patients also report them to be unsightly and hinder some in functional tasks, for example dressing. Synergies are not measured in clinical practice however research studies have attempted to quantify them. This is mostly performed with EMG during activity but can only be observed in severely impaired individuals (Cheung et al., 2009, Roh et al., 2013). Isometric force-matching tasks (Dewald et al., 1995) have better quantifying abnormal control than antigravity movements (Barker et al., 2009, Cheung et al., 2009, Prange et al., 2010). In reaching movements, when gravity is eliminated, normal activation patterns are maintained in mild to moderate affected stroke patients (Coscia et al., 2014) thereby allowing practice of 'normal' reaching.

The underlying causes for the co-contraction observed in stroke patients can be difficult to tease apart and are still not well understood (Tropea et al., 2013). Possible mechanisms could include co-activation due to extensive remapping leading to activation of widespread cortical areas

(Johansen-Berg et al., 2002, Ward et al., 2003), changes in the spinal interneuronal excitability, or increased reliance on brainstem and particularly reticulospinal pathways. RST reliance could explain some of the features observed in the upper limb after stroke. Evidence in humans is still limited however animal models suggest that the less divergent motoneuronal projections could explain decreased individuation of movement control (Matsuyama et al., 1999). Additionally the RST projections to upper limb flexors after a stroke are more numerous and excitable in animal models (Ellis et al., 2007, Ellis et al., 2012, Zaaimi et al., 2012).

Movement at any joint results in altered rotational forces at adjacent joints. In single joint movements these forces are overcome and the limb stability is maintained by altered phasic muscle activation and are achievable after stroke (Gribble and Ostry, 1999). However most functional arm movements require movement not only around one joint, but also as multi-joint movements. In multi-joint movements significant interaction torques arise not only due to the muscle action at the joints but also due to the interaction of the movement of other segments (Hollerbach and Flash, 1982). Despite these altered inter-segmental dynamics, in healthy individuals movement trajectories are preserved at different velocities and with different arm configuration (Hollerbach and Flash, 1982). Changes in electromyograph (EMG) activity, to adjust movement, depending on these torques, are observed too early to allow for spinal or supra-spinal feedback, effecting corrections of the motor command and therefore indicate that these alterations in torques are computed in a predictive manner (Cordo and Nashner, 1982). After stroke normal kinematics of multi-joint movements are however not preserved and the trajectories and accuracy of movements deteriorate (Levin, 1996).

Movement impairments after stroke result from a combination of these and other impairments. Measurements to quantify each impairment is important, however, the contributions of the individual impairments are difficult and possibly impossible to tease apart because they are inter-related and impact on each other.

2.3. Neuroplasticity

In animal models it has now been firmly established that the central nervous system can recover from an insult. The exact mechanism of recovery is unclear although neuroplasticity through Hebbian learning appears the most likely mechanism (Nudo, 2011). Neuroplasticity is described as a: 'Change in strength of synaptic connections in response to either an environmental stimulus or an alteration in synaptic activity in a network' (Murphy and Corbett, 2009). In the acute period after neurological insult, spontaneous recovery occurs through a combination of structural and functional processes (Murphy and Corbett, 2009). The restoration of oxygen supply to the infarcted area through angiogenesis can prevent further cell death in the penumbra and reduction of peri-infarct oedema results in the resolution of diaschisis (Nudo, 2011). Injury triggered neurogenesis leads to homeostatic changes via exogenous growth promoting agents and alterations in neurotransmitters levels (Krakauer et al., 2012). Further recovery is experience dependent, partly via sensory input or through skill acquisition due to training (Nudo, 2006).

Translation of this knowledge derived from animal studies to recovery processes of human stroke survivors is increasing (Krakauer et al., 2012, Carmichael and Krakauer, 2013). Evidence of the exact processes that underlie recovery for different interventions at various time points is however difficult to establish (Buma et al., 2013). Recovery of decreased upper limb function after a stroke involves the a reacquisition of movement and has been likened to a skill learning process (Kitago and Krakauer, 2013). Skill can be relearned by recovering lost function, using the same effectors to perform the movement, or by applying compensatory strategies where other effectors or altered movement patterns are used to achieve the goal (Levin et al., 2009, Buma et al., 2013). Although both of these processes require synaptic change the former is the prime rehabilitation target when attempting to restore pre-insult functional ability. In animals it has been demonstrated that a period of heightened plasticity is evident early after a neurological insult, and result in most of the peri-infarct and remote remodelling and recovery (Krakauer et al., 2012). It is presumed that the same

holds for recovery in humans but direct evidence for the same processes and time-frames are difficult to gather.

In animal models training results in surprisingly fast structural changes in neural structures, such as alterations in dendritic branching, axonal sprouting, and formation of new synaptic connections (Abbott and Regehr, 2004). In addition training can result in extensive remapping of the cortex where other areas of the M1 have been shown to take over the function (Nudo et al., 1996). The combination of these processes lead to an improved ability to form and relay the motor command to the musculature and achieve the specific movement goal. Factors promoting this process include sufficiently challenging tasks (Lotze et al., 2003), and intensive training to increase secretion of brain derived neurotrophic factor (BDNF) (MacLellan et al., 2011) as well as the stimulation provided by the environment (Biernaskie et al., 2004). This recovery process is very promising however the conclusion that it occurs in a similar fashion and time-frame in humans and more relevantly in an older population of individuals affected by stroke has to be made with care.

When proximal upper limb muscles are weak after stroke, in addition to the recovery mechanisms described above, other recovery pathways can be relied upon, as the innervation of these muscles does not rely solely on an intact corticospinal tract but also on bilaterally projecting reticulospinal pathways and the ipsilateral CST (Schepens and Drew, 2006, Lemon, 2008). Zaimi et al, demonstrated increased responses in limb flexors due to brain stem stimulation in lesion studies in Macaque monkeys (Zaimi et al., 2012). The effectiveness of targeting this pathway in human rehabilitation and the resulting recovery processes has however not been investigated.

2.4. *Promoting recovery*

Rehabilitation of the upper limb after a stroke is aimed at improving functional ability in an attempt to optimize quality of life and independence. Intensive therapy especially in the acute phase with specialist, multi-disciplinary care and training improves outcome (Langhorne et al., 2014).

Stroke patients can re-acquire motor skills to some extent even many months after the original insult via similar mechanisms of motor learning as healthy subjects aimed to prime existing connections, form new synaptic connections and promote axonal growth, a process known as neuroplasticity (Di Filippo et al., 2008). Although direct evidence of neuroplastic change in human subjects is difficult to ascertain, changes in activation patterns on fMRI (Scholz et al., 2009) and diffusion weighted MRI (Bosnell et al., 2011) as well as TMS connectivity changes (Barker et al., 2012), are indicative that neuroplasticity is the underlying process.

Therapy is broadly focussed to either address motor impairments, i.e. weakness, muscle length changes, and motor coordination, and sensory re-education, or, at activity level, namely task specific practice. Current evidence supports the use of task-specific practice to increase functional ability as it has a strong evidence base, specifically when used in the form of constraint induced movement therapy (CIMT) focussing on distal upper limb recovery in mildly affected stroke patients (Lang et al., 2013, Langhorne et al., 2014). However a great proportion of stroke survivors are more severely affected and are unable to move their wrist or fingers, and present with no functional distal movement and proximal weakness (Royal-College-of-Physicians, 2013).

For task-specific practice, sufficient muscle activation needs to be possible to perform the practised task. If the severity of the impairment prevents the completion of a task, and, for example, the shoulder flexors are too weak to lift the arm for a reaching task, the task either will be performed using other body segments and promote compensatory movement strategies (Corti et al., 2012), or needs to be broken down into achievable sub-sections of the task. If the task is broken down improvements can be achieved at an impairment level which can lead to a restoration of motor control (Ada et al., 2006, Corti et al., 2012). Task specific practice can then be commenced when the impairment is reduced, allowing completion of the task. In this study I trained individuals with proximal upper limb weakness to perform supported reaching movements, to reduce task difficulty. The testing and training protocol was tailored to each individuals reaching speed ability.

2.4.1. *Timing of trials and interventions*

The optimal timing of therapeutic interventions in humans affected by stroke is thought to be within the first 3 months after insult, based on evidence from animal studies that show a brief window of heightened plasticity between roughly 5 days to 3-4 weeks post infarct (Carmichael and Krakauer, 2013). It is generally assumed that stroke patients also recover through this neuroplastic process and that therapy enhances this process (Buma et al., 2013), but some research groups propose that very little true recovery occurs in stroke patients and that improvements in upper limb function are due to compensatory strategies (Zeiler and Krakauer, 2013). Evidence of a variety of therapeutic interventions addressing impairments argue against this (Buma et al., 2013, Langhorne et al., 2014), however the proposition that rehabilitation in the acute stage should be aimed at restoration of normal function by attempting to normalise activity with reliance on the lesioned hemisphere are valid (Zeiler and Krakauer, 2013). However limiting chronic interventions to compensatory strategies to optimise participation (Zeiler and Krakauer, 2013) would be detrimental because improvements at an impairment level (Eng, 2004, Barker et al., 2009) as well as in activities of daily living (Lang et al., 2013) have been clearly demonstrated in this population. However, in this phase other factors besides neuroplasticity might contribute to the observed improvement in function. Reversal of learnt disuse, strengthening of atrophied muscles and improved biomechanical properties of the muscle induced by training could all provide the additional mechanisms to plastic changes induced in the neural system (Barker et al., 2009).

The point at which therapy should be terminated is equally unclear. After stroke it is often recommended that therapy should finish when patients reach a plateau and fail to respond to rehabilitation. However, this may be partly the result of adaptation to a therapy programme, as seen in healthy subjects performing an exercise regime over time. Further improvements may be observed after a modification in intensity and/or specific intervention.

As recovery is the greatest early after a stroke it can be difficult in this period to clearly demonstrate if improvements after a therapeutic intervention in humans are due to spontaneous recovery or if they are experience dependent (van Kordelaar et al., 2013). Therefore rehabilitation trials are frequently performed in the chronic period (Stinear et al., 2013) when a plateau of functional ability can be assumed.

2.4.2. *Impairment based therapy*

It is intuitive that the severity of impairment and functional ability should be related. However evidence that impairment focussed intervention enhances neurological function in individuals affected by stroke is still not very strong (Langhorne et al., 2011).

The long held belief that strengthening and high intensity training increases spasticity (Bobath, 1979) in individuals affected by stroke has been shown to be unfounded. It is now clear that strengthening interventions increase muscle strength and improve activity after stroke (Carr and Shepherd, 1983, Ada et al., 2006, Harris and Eng, 2010, Patten et al., 2013). Strengthening training can lead to more restoration of movement patterns (Corti et al., 2012), and additional improvements may become evident as increased muscle power enables incorporation of the upper limb into function and thereby increase activity and strength further. Additionally, retained improvements in biceps brachii stretch reflex modulation have been reported after intensive training programmes (Schmit et al., 2000).

The effect of strength training on the underlying impairment and on functional recovery does however differ in the recovery phases. In the acute period following a stroke reduced force production is due to a loss of descending input to the spinal motor neuron. However in later phases longstanding alterations in activation patterns, a reduction of the cross-sectional muscle bulk due to atrophy and a reduction of motor units due to disuse play an added role (Ramsay et al., 2011).

The exact mechanism of improvements of performance after strength training, are still not completely understood (Barker et al., 2009). Evidence in healthy individuals indicate that training can alter cortical excitability, not only by increased it but also by a reduction of cortical inhibition and increased efficiency of muscle activation patterns presumably by an improved motor command (Carroll et al., 2002). A similar mechanism is presumed to be underlying the changes in performance observed in the acute stages after stroke (Wagner et al., 2007). In the chronic phase strengthening, in addition to neuroplasticity, a core driver of learning, present at all times in health and disease, leads to structural and physiological changes in the disused muscle, improving firing patterns and muscle metabolism (Wagner et al., 2007, Barker et al., 2009) similar to changes observed in healthy individuals after training (Carroll et al., 2011).

Neural contributions to hypertonia, caused by an increase in stretch reflex evoked muscle activity (spasticity), are amenable to pharmacological interventions (Bakheit, 2012). Maintenance and restoration of muscle length and muscle compliance is vital in the management of hypertonia as well as in people with muscle weakness who are unable to voluntarily move their joints through full range. Physical interventions for hypertonia focus on the non-neural contributions to tone, resulting from an increase in the resistance offered by the intramuscular and peri-articular connective tissue and include stretching and splinting techniques (Pandyan et al., 2005). Although limited evidence is available of the effectiveness this is normally done using a variety of techniques including active and passive stretches, casting and orthoses (Katalinic et al., 2010).

Increasing the focus of rehabilitation programmes on impairment promotes restoration of movement patterns but the necessary components for optimal practise are still not clear. Inclusion of motor learning principles in these programmes is however a promising development.

2.4.3. Motor learning

The mechanism of motor learning, or operant conditioning can be defined by Thorndike's Law of effect: *'Of several responses made to the same situation, those which are accompanied or closely*

followed by satisfaction to the animal will, other things being equal, be more firmly connected with the situation, so that, when it recurs, they will be more likely to recur; those which are accompanied or closely followed by discomfort to the animal will, other things being equal, have their connections with that situation weakened, so that, when it recurs, they will be less likely to occur. The greater the satisfaction or discomfort, the greater the strengthening or weakening of the bond.' (Thorndike, 1911).

Motor recovery after a neurological insult is believed to be a learning process in which individuals aim to improve their performance at a given task, leading to the acquisition of increased skill at a motor task. Mazzoni et al, suggested that movement skill can be detected in improvements in the speed-accuracy relationship of skilful movements (Fitts, 1954). Studies in healthy individuals indicate that training allows a shift in this trade-off so that more accurate, efficient movements can be performed at a greater velocity (Reis et al., 2009, Shmuelof et al., 2012).

Becoming skilful at movement further results in a reduction in spatial and temporal variability of reaching movements after repetition and learning (Georgopoulos et al., 1981, Verstynen and Sabes, 2011).

Through a combination of evidence gained in healthy individuals, stroke patients and animals studies it is clear that the training structure of therapy protocols, including motor learning concepts, are very important (Kantak et al., 2010, Schmidt and Lee, 2011) and movement repetition is central to achieving learning (Langhorne et al., 2009, MacLellan et al., 2011). Additionally the challenge of the task (Lotze et al., 2003, Krakauer et al., 2005), the environment in which therapy is delivered (Janssen et al., 2014), distribution of training (Kantak et al., 2010) and the structure of feedback of results (Cirstea et al., 2006, Subramanian et al., 2010) all influence learning . Practice intensity found to be effective for acquisition of a motor skill in animal studies (Georgopoulos et al., 1981, Nudo et al., 1996) is however seldom achieved in clinical practice. Observational studies of stroke rehabilitation demonstrates that repetition of any movement in stroke patients tends to be much

lower (Lang et al., 2009) than the 400 repetitions which were found to be effective in animal studies (Nudo et al., 1996, MacLellan et al., 2011). As the importance of increased intensity of training has been recognized a number of upper limb research studies report high repetition training but even in these trials reaching movements involved only 60-120 reaches per session (Barker et al., 2008, Duff et al., 2013, Subramanian et al., 2013). It has however been shown in a proof of principle studies that 400 movement repetitions are achievable in stroke patients (Birkenmeier et al., 2010, Milot et al., 2014).

In a literature review it was found that on an average stroke patients spend only 4.2 minutes a day on upper limb rehabilitation during their acute inpatient stay (Hayward and Brauer, 2014). In the acute stage, rehabilitation emphasis is placed on independent mobilisation to facilitate discharge, and the window of heightened plasticity, presumed to be similar in human as in animals, (Carmichael and Krakauer, 2013), to promote neuroplastic recovery of the upper limb might be missed. This could result in upper limb movements being performed with a reliance on compensatory strategies to achieve tasks of daily living (Levin et al., 2009, Krakauer et al., 2012).

Motor learning occurs over a period of time and time scales. The improvement can be observed during the learning period (on-line) or further improvements can be seen after the training (off-line) (Schmidt and Lee, 2011). These offline gains are probably due to consolidation of the newly acquired ability, a stabilization of the motor memory, which makes it resistant to interference by subsequent similar stimuli (Krakauer, 2006, Lin et al., 2010).

2.4.4. *Types of motor learning*

Proposed learning mechanism can be divided into two categories, model-based and model-free approaches (Huang et al., 2011). Model-based learning is based on subconscious changes of the forward model by sensory prediction error; the cerebellum is a vital contributor in this process (Galea et al., 2011). In contrast model-free learning requires trial and error exploration as described by Thorndike's Law, 1911 (Sutton and Barto, 1981).

A variety of learning paradigms are used to investigate motor learning in healthy individuals. Model-based adaptation paradigms investigate movement changes when either feedback of performance (visuo-motor learning) or motor performance (force-field learning) is manipulated and result in a movement error (Krakauer and Mazzoni, 2011). To reduce the error signal encountered due to this manipulation, individuals alter their performance to return to an error free state, for example when using a computer mouse with an altered gain. The amount of adaptation (motor learning), achieved is measured by the size of the after-effect seen when the manipulation of the feedback or movement is removed. This after effect quickly washes out.

Although the findings in these model-based paradigms add valuable information about motor learning mechanisms they describe quite a different learning process than the challenge of reacquiring a movement skill after a neurological event like a stroke (Krakauer and Mazzoni, 2011). In these circumstances, in contrast to adaptation, motor skill requires learning a new model-free movement and then repetition to produce greater efficiency in its performance (Shmuelof et al., 2012). Use-dependent learning is model-free and repetition of a specific movement alters the habitual preference and a bias emerges which attracts consecutive movements to a similar movement pattern (Diedrichsen et al., 2010). This can be observed as a spatial convergence onto the practised path (Diedrichsen et al., 2010, Huang et al., 2011, Verstynen and Sabes, 2011) or as a preference to move at a practised movement speed (Hammerbeck et al., 2014).

2.5. *Generalisation to other task demands*

Generalisation or transfer of performance is the ability to apply improvements of task performance due to training to similar novel behaviours (Poggio and Bizzi, 2004, Censor, 2013). In rehabilitation, generalisation is of great interest because the effectiveness of interventions is measured as an ability to carry over the improvement achieved during training on a specific tool to improvements in clinical scales and ultimately to activities of life. Generalisation has been observed in healthy individuals between the left and right arm in an adaptation study (Joiner et al., 2013) and

for reaching movements from holding a robot arm to unsupported reaches (Kluzik et al., 2008). Unsurprisingly, generalisation is greater when scaling to smaller but not larger than practised parameters (Mattar and Ostry, 2010) and does not transfer well to greater complexity of movement (Wulf and Shea, 2002, Kantak et al., 2011). Evidence investigating this kind of generalisation in stroke survivors is very limited.

Another interest in rehabilitation is the ability to improve performance for a movement to different locations in space that requires a similar but not identical muscle subset as the trained movement. Here activity patterns of muscle subsets, and therefore neuronal ensembles, have to be scaled and weighted differently in intrinsic muscle and joint movement configurations (Churchland et al., 2012). Most of the work investigating this has been performed in adaptation paradigms in healthy individuals. When feedback of the trajectory was provided during the reaching movement, generalisation was only observed when the target location was relatively similar, and required a similar trajectory (Thoroughman and Shadmehr, 2000). If however feedback only consisted of the endpoint of the movement, the learned behaviour did generalise broadly to other locations in space (Malfait et al., 2002).

Movement difficulty and joint torques are influenced by movement speed (Moran and Schwartz, 1999, Sukal-Moulton et al., 2014), which poses the question if newly acquired skill could be performed at non-trained movement speed? Interestingly generalisation to non-trained movement speeds has been found to be broad when performing skilful wrist rotations (Shmuelof et al., 2012). The interaction torques during reaching movements are however much greater (Beer et al., 2000) and generalisation to other movement speeds has only been investigated in adaptation paradigms. In this study in healthy individuals generalisation was scaled to the force of the perturbation as well as the speed (Goodbody and Wolpert, 1998).

The structure of the learning process is likely to be crucial in determining if the improvement in behaviour generalises (Censor, 2013). Generalisation is thought not to rely on a fixed motor plan

or synaptic ensemble but on the use of muscle subsets during the motor learning process. By adjusting the weighting of these subsets to altered task demands the learned behaviour can be applied to novel situations (Poggio and Bizzi, 2004). Generalisation of learning varies greatly depending on the learning paradigm, and the pattern of generalisation can provide insights into the learning mechanism (Shadmehr, 2004). Other factors influencing the amount of generalisation observed are the number of degrees of freedom (DOF) that are not fixed during the acquisition of skill. For example, when reaching to a target with limited DOF (i.e. elbow and shoulder flexion and extension) while holding onto a manipulandum vs. reaching unconstrained to point at the target with a finger, the increased redundancy during the acquisition phase provides the adaptability needed for generalisation to altered demands (Yang et al., 2007, Park et al., 2013). Smaller trial-by-trial errors, and thereby a more consistent movement pattern during the acquisition of a skill, has been shown to be conducive to generalisation (Kluzik et al., 2008).

2.6. Predictors of recovery

Recovery patterns after stroke are understandably variable due to the nature of the disease. Previous studies have established that the severity of hemiparesis is the best predictor of recovery (Kwakkel et al., 1996), but still great variability remains. With greater knowledge about each individuals' recovery potential, patients could be stratified in clinical trials and in clinical practice to receive the therapy, most likely to optimise rehabilitation potential (Cramer, 2010, Carmichael and Krakauer, 2013).

The functional ability of individuals in the acute stage can however predict recovery very well (Prabhakaran et al., 2008). Further prognostic studies, investigating upper limb recovery in human stroke survivors, have been able to predict outcome at 3 and 6 months very reliably (Stinear, 2010, Stinear et al., 2012). The presence of wrist and finger movements as well as intact corticospinal connections, established with transcranial magnetic stimulation (TMS), indicate a good recovery potential of hand function. Corticospinal tract output determined by TMS is a better

indicator of recovery potential than lesion extent (Ward et al., 2007) or lesion site (Swayne et al., 2008).

Longitudinal fMRI studies have demonstrated that normal activation patterns of the stroke hemisphere, when moving the affected upper limb predict the best recovery. Extensive activation of the non-affected hemisphere during these movements predict poor recovery of functional hand movement (Ward et al., 2003). There appears to be a hierarchical functional architecture in which the function of the damaged motor cortex is preferentially substituted by the ipsilesional pre-motor cortex, and then by the contralesional premotor cortex (Johansen-Berg et al., 2002, Swayne et al., 2008). Recently, this over-activity in the non-affected hemisphere has been receiving greater attention, to investigate if this re-organisation of motor pathways is functionally relevant. It is thought that after more severe lesions, when the CST integrity is compromised, reliance on bilateral RST by the non-affected hemisphere is up-regulated (Lemon, 2008) for activation of the affected limb as has been observed in animal studies (Bradnam et al., 2011, Fisher et al., 2012, Zaaimi et al., 2012). The reticulo-spinal tract is however not as specialized and converges on multiple levels in the spinal cord, connecting with multiple motor neuron pools (Matsuyama et al., 1997). Therefore recovery reliant on this tract could result in less refined movement patterns and resultant mass-activation. This mechanism could explain the limited improvement in fine hand movement observed by Ward et al, (2003). The reticulospinal tract has however been shown to be able to assist in more gross movement patterns, like reaching in animal studies (Schepens and Drew, 2004, 2006). Another possible pathway to mediate muscle activity in upper limb reaching movements, is the C3/4 propriospinal pathway with divergent innervation across joint levels (Roberts et al., 2008).

The presence and effectiveness of these different connections can be studied using single pulse TMS of the motor cortex of each hemisphere (Schwerin et al., 2008, Barker et al., 2012). In stroke, more severely affected individuals demonstrate a greater reliance on ipsilateral projections from the non-stroke hemisphere (Schwerin et al., 2008). Indeed, this connection appears to be

stronger than in healthy individuals (Turton et al., 1996, Alagona et al., 2001), suggesting that recovery may promote recruitment of these connections in order to optimise function. Cortical inputs from the non-stroke hemisphere are also important for recovery of swallowing function in dysphagic patients after stroke. TMS studies have shown that pharyngeal and upper oesophageal muscles receive a bilateral innervation from motor cortex. Following stroke, recovery from dysphagia depends on increased excitability in the pathway from the non-stroke hemisphere (Jayasekera et al., 2010). There might be potential to exploit this pathway in stroke patients with proximal weakness to improve arm control (Bradnam et al., 2013).

2.7. *Assessing cortical connectivity*

Transcranial magnetic stimulation (TMS) is a non-invasive technique to measure specific brain circuitry. It uses electromagnetic induction to generate a weak electric current, at a right angle, in the underlying tissue. When the stimulation is administered over the primary motor area (M1) of the scalp, the underlying neurons are depolarised and an action potential is discharged. With sufficient summation of multiple motor neurons, a motor evoked potential (MEP) can be detected and measured by electromyography (EMG) of the representative underlying muscle (Day et al., 1989).

This procedure is particularly well established in healthy individuals for distal upper limb muscles which have large cortical representational areas (Rothwell et al., 1987). It can also be performed in stroke patients to assess the integrity of descending pathways by stimulating the affected and unaffected cortex. Connectivity to the hemiparetic limb can be established via both direct CST and indirect pathways (Lemon, 2008). Contralateral responses from the affected hemisphere after stroke are smaller due to interruptions in corticospinal drive. The emergence of ipsilateral responses from the affected hemisphere was thought to be an indication of direct connections but this has now been largely refuted (Palmer et al., 1992). These connections could be an expression of up-regulated RST, which is promoting recovery however studies are divided of the

importance of this tract in recovery. The importance of this tract to motor function has been demonstrated by impaired function in more severely individuals after cathodal transcranial direct current stimulation (tDCS) to the unaffected hemisphere (Bradnam et al., 2011) however, Barker et al, found that these pathways did not contribute to recovery (Barker et al., 2012). To investigate connections to proximal limb muscles in stroke patients (Schwerin et al., 2008, Bradnam et al., 2011, Barker et al., 2012) muscles need to be pre-activated (Alagona et al., 2001, Bawa et al., 2004, MacKinnon et al., 2004) and stimulus intensities need to be increased (Schwerin et al., 2011). The contribution of the two hemispheres to movement, or MEPs, can be expressed as a laterality index (Schwerin et al., 2008).

2.8. Movement speed

After neurological disease (Mazzoni et al., 2007, DeJong et al., 2011), also in healthy ageing (Gill et al., 1997), movements tend to be slower. Rehabilitation paradigms targeted at improving proximal upper limb movements after a neurological insult are not specifically designed to alter or increase movement speed and thereby potentially reinforce the slowness of movement. Fast movements are avoided in rehabilitation probably because of the velocity dependence of spasticity (as highlighted in Chapter 2.1,(Pandyan et al., 2005), with potential deleterious effects on movement quality (Bobath, 1990) and movement control (Graham, 2013). However it has also been reported that very slow movements are difficult for stroke subjects, and result in increased jerk and less symmetry in the velocity profiles (DeJong et al., 2011). In the presence of substantial muscle weakness, faster movements can be easier to initiate and maintain by the use of mass activation patterns (DeJong et al., 2011).

Scales used in clinical trials are often not sensitive enough to detect change induced by training (Buma et al., 2013). This study proposes a new approach to describe the changes in motor control that account for therapeutic gains (Mazzoni et al., 2007). Other authors have quantified improvements in upper arm reaching in terms of normalisation of joint coordination, speed of

movement, curvature of movement etc. (e.g. (Caimmi et al., 2008)). All of these are valid measures but are generally inter-related. This study introduces a new method for quantifying skill learning, and uses this to test the effectiveness and generalisation of two training protocols. The method stems from Fitts' (Fitts, 1954) observation that there is a trade-off relationship between speed and accuracy during skilled movement.

This measure of performance can be adapted to a wide variety of tasks. Skill learning in this scheme is represented by a shift in the relationship such that as skilful performance improves, movements of a given accuracy can be made at a higher velocity, or movements at a given velocity can be performed with greater accuracy. This can be quantified using a simple mathematical manipulation into a skill learning parameter which Reis et al, (Reis et al., 2009) have shown can reliably detect changes in movement performance due to training in healthy subjects. Such quantification has an important secondary benefit. It helps us to standardise the physical training by telling us the average movement speed at which an individual can make a movement of given accuracy. Training can then be formalised by challenging subjects to perform movements at the same speed but with greater accuracy than their speed-accuracy curve would predict.

The aim was to compare the effect of slow (Fig 2.1A) versus fast movement speed during training on the form of this curve (Fig 2.1A). The curve will allow me to say how well the training generalises outside of the trained movement speed. Local improved accuracy would signal training speed specific improvements (Fig 2.1B); namely improved accuracy at the slow speed for the slow training group (i) and at fast speed for the fast training group (ii). Generalised improvements (Fig 2.1C) would indicate that training reaching at the given speed improves reaching accuracy for all other speed-accuracy requirement combinations.

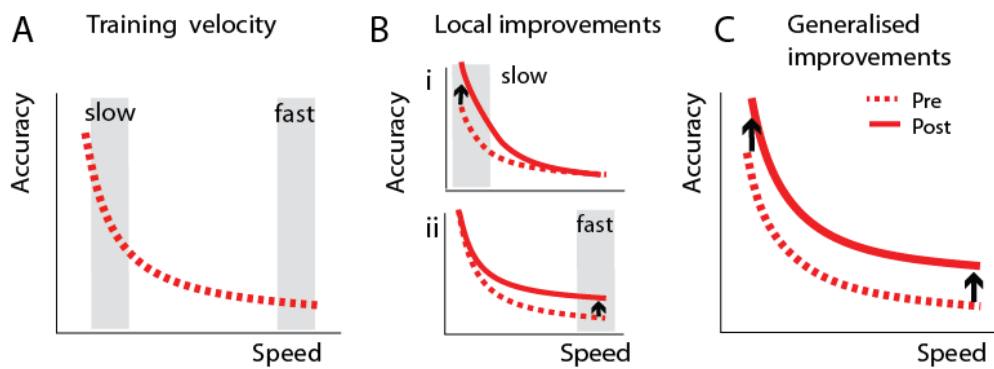


Figure 2.1. Speed-accuracy relationship. A) Demonstrating training at either slow or fast movement speeds. B) Indicating local, speed-specific improvements and i) slow movement speed and ii) at fast movement speed. C) Showing generalised improvements at slow and fast speed as well as all other SAT combinations.

2.9. Outstanding questions

Rehabilitation is performed at slow movement speed with an emphasis on improving movement accuracy, however, activities of daily life require fast movements, for example crossing a road. During fast movement, joint torques is altered as well as the ability to rely on feedback of movement performance. Whether training at slow movement speed also improves stroke patients' performance at fast speed is not known.

I therefore designed a training protocol to test learning of fast and slow reaching movements in chronic stroke patients and how this generalised to other movement speeds along the speed-accuracy trade-off function.

Traditionally high number of movement repetition and fast movements have been avoided in rehabilitation due to a fear of increased abnormal muscle synergies and spasticity, it is now clear that a high number of movement repetition is not detrimental to stroke patients but this is still not established about movements at high speed. I investigated if training at high velocity is detrimental to chronic stroke patients on an impairment and kinematic level.

Another unresolved question is regarding the role of the RST in proximal upper limb recovery after stroke. An increased reliance on this pathway is proposed in stroke patients, particularly for proximal muscles and upper limb flexors. I used neurophysiological techniques to assess the patients' reliance on the CST and RST for upper limb control and alterations to these pathways due to training.

Additionally I performed a pilot study on healthy individuals to assess the performance and amount of learning at different movement speeds. I investigated the effect of repeated exposure of a specific movement speed on the habitual movement speed after training.

3. General Methods

3.1. Subjects

Experimental and consent procedures were approved by the Joint Ethics Committee of the Institute of Neurology, UCL, and the National Hospital for Neurology and Neurosurgery, UCL Hospitals NHS Foundation Trust, London.

3.1.1. Healthy

Eighteen healthy adults without a history of upper limb neurological or musculoskeletal disorder attended for 5 consecutive days.

3.1.2. Stroke patients

Patients were recruited from the National Hospital for Neurology and Neurosurgery, London and from the community via advertisement on charity stroke clubs and websites. Potential participants were screened by UH and then referred to the Institute of Neurology, London, UK. Thirty-seven individuals affected by stroke (See table 5.1) without a history of a previous stroke or other concomitant neurological or musculoskeletal disorder attended for six days. Initial assessment was performed at the end of week one and they attended for the 5 consecutive days of the next week. All patients had had their stroke more than one year previously, and presented with persistent upper limb weakness of the triceps and/or anterior deltoid muscles (≤ 4 on the Medical Research Council muscle power scale) but were able to perform the experimental task consisting of at least a 15 cm supported reach in the robotic manipulandum. Exclusion criteria consisted of i) proximal upper limb spasticity greater than 2 on the Modified Ashworth scale, ii) severe sensory impairment ($< 50\%$ accuracy on 1g monofilament sensory testing on dorsum and palm of hand and $> 5\text{mm}$ - 2 point discrimination task on the index fingertip), iii) shoulder pain greater than 3/10 on a continuous self-rated visual analogue scale, iv) uncorrected visual impairment and /or v) cognitive and language impairment, impeding with co-operation in the study protocol.

All patients gave written consent to the study in accordance to the Declaration of Helsinki.

3.2. Clinical examination of stroke patients

A clinical evaluation was conducted by a neurologist (DH), blinded to the patient's randomization to training group, on the first and last day of attendance. The examination consisted of measuring performance on the Fugl-Meyer upper limb subset (Fugl-Meyer et al., 1975). Additionally, measures of biceps, triceps, anterior deltoid and pectoralis major muscle power were established using the Medical Research Council muscle power grading system (Kendall McCreary et al., 2010). Spasticity of the affected upper extremity was measured for the elbow flexors, extensors and wrist flexors while seated in a supportive chair using the modified Ashworth scale (MAS). In this scale passive movements of flexion and extension are graded between 0 (no stiffness) to 4 (fixed contracture) (Bohannon and Smith, 1987). Because of the non-linear distribution of points along this scale we converted scores to a 6 point scale (0-5) for analysis (Pisano et al., 2000). In clinical practice the MAS is the most frequently used measure to grade spasticity. Although it is not very sensitive it is reliable and reproducible (Bohannon and Smith, 1987, Gregson et al., 1999).

Additionally, the participant's pre-stroke handedness was established with the Edinburgh handedness scale (Oldfield, 1971) and sensory testing consisted of a descending two-point discrimination task on the distal aspect of the affected index fingers (5-3mm), and ability of detecting light touch sensation on the dorsal and palmar aspect of the wrist using a 1g sensory testing monofilament (Bailey©) (<50% accuracy severely affected and excluded, >50% & <80% mod affected, >80% accuracy no/mild affected).

3.3. Workspace

Each individual's ability to move their affected arm was measured when gravity was eliminated and with gravity acting on the upper limb, as a measure of functional workspace (Beer et al., 2007, Ellis et al., 2009). Individuals were seated in front of a table with a smooth high-gloss, polished polyester gel-coat finish. Their trunk was restrained and the affected hand and forearm were positioned pronated on a low friction material on the starting box in midline. The shoulder

was positioned at 15° shoulder abduction and flexion while the elbow was at 90° flexion. The chair height and position was documented, and positioning was reproduced for follow-up measurements. A movement tracker was positioned on the ulnar styloid process, and the position of the table in relation to the camera was calibrated. Individuals were instructed to perform the largest possible circular movement while maintaining hand contact with the table. This procedure was repeated three times in a clock-wise, and then three times in an anti-clockwise direction. The chair height was then increased by 3cm and movements were performed with the hand and forearm hovering just over the table (12 movements in total; 6 supported & 6 unsupported).

Movement data were acquired using a Polaris Vicra NDI System with a sampling rate of 20Hz. Data traces were transformed to represent data in a horizontal plane with standardised Cartesian coordinates. Only data points anterior of the starting point were used for analysis as the task instruction requested moving the arm on the table and training emphasized forward reaching movements. Because the starting position was on the table, just anterior of the sternum, any movements posterior would not be supported anymore. To standardize measurement technique between supported and unsupported reaching movements we also only investigated movement anterior of the starting position for the unsupported reaches. For performance analysis the maximum excursion in the y-direction was extracted from the 3 repetitions of each task. Successful trials for the unsupported reaches were defined, as movements where no contact was made with the table. Unsuccessful trials were discarded.

3.4. *Reaching paradigm in robotic manipulandum*

Participants were seated with their forehead supported on a headrest. Their semi-pronated right hand gripped a manipulandum underneath a horizontally suspended mirror. The mirror prevented direct vision of the hand and arm, but showed a reflection of a computer monitor mounted above, that appeared to be in the same plane as the hand (Fig 3.1).

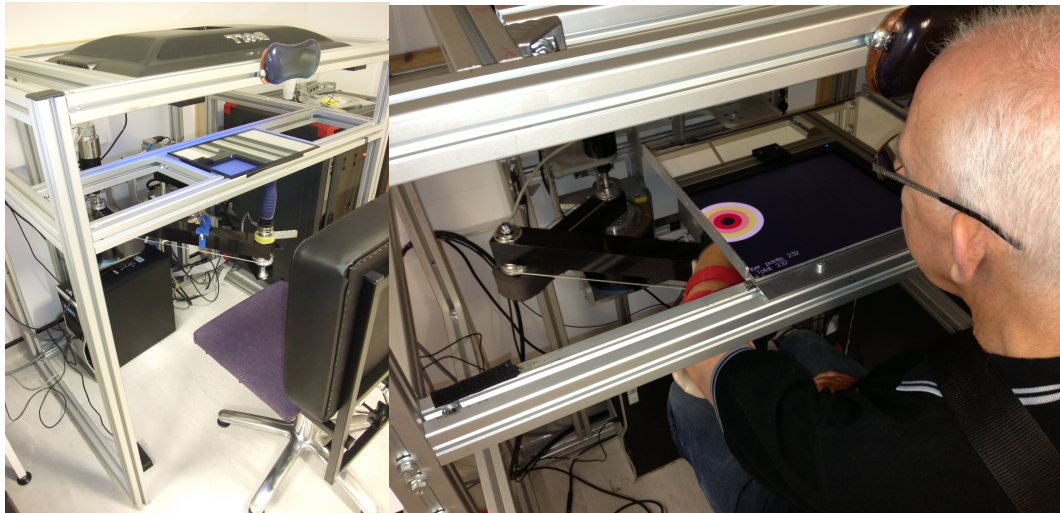


Figure 3.1. Manipulandum and experimental set-up

The visual display (Fig 3.2A) comprised a 1 cm diameter starting box, a green cursor (0.5 cm diameter) representing the position of the manipulandum and a circular 10 cm diameter target with a small black cross at its centre, which was located 25cm in healthy and 20cm for stroke participants, from the start box at an angle of either 0 or 45 degrees. At the start of a trial a motor moved the participants' arm, and thereby the cursor into the start box presented in midline. The gleno-humeral joint was in ~30 degrees of elevation through flexion, and 45 degrees of abduction, and the elbow at ~ 90 degrees flexion.

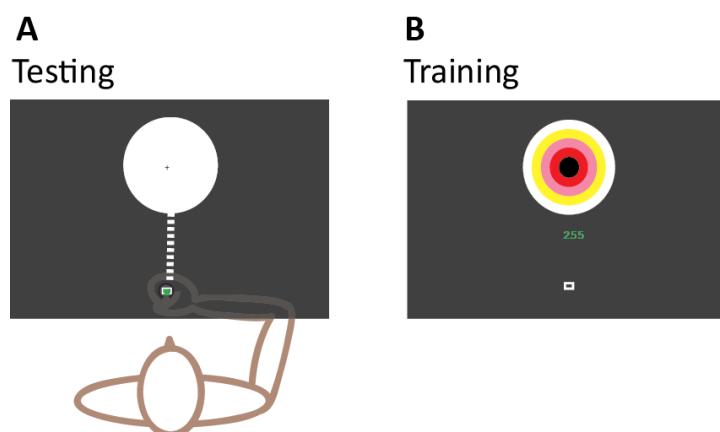


Figure 3.2. A) Experimental display during pre- and post-testing with target centred 20cm at 0 degrees. B) Bull's-eye scoring system during training blocks.

Participants were instructed to start moving in their own time after the start signal. At movement onset the cursor disappeared, and reappeared, showing the hand position, at the end of the movement. Reappearance of the cursor indicated the end of the trial and provided feedback of reach end-point accuracy. The reaching paradigm differed between healthy individuals and stroke patients.

3.4.1. *Healthy participants*

In healthy participants the duration of each trial was identical irrespective of the allowed movement time (i.e. 2320ms). The starting signal, a change from the target (Fig. 3.2A) from an outline to a solid colour, appeared 100ms after trial initiation. At movement end, feedback was displayed for 300ms after which the robotic manipulandum moved the arm back to the starting position. The hand was held in the starting position until the end of the trial time (2320ms). This means that shorter movement times therefore had longer wait times at the end of a trial for initiation of the next trial. Reaction time was not enforced and was not included in the trial time. Participants familiarized themselves with the task by performing 10 reaches with continual visual feedback at 900ms and 300ms as well as 10 reaches without visual feedback at 300ms.

3.4.2. *Stroke patients*

I altered the protocol in regards to how movement endpoint was determined before performing the study in stroke patients. Stroke patients had to stop moving in a pre-determined movement time (See 3.5.2 for how movement time was determined). As described in the background section motor learning can be investigated in health and disease with a number of paradigms (Krakauer, 2006). This reaching task was designed to be a skill learning paradigm (Kitago and Krakauer, 2013) which closely resembles the relearning of movement control required by individuals affected by stroke, in improving independence in daily functional tasks.

The starting signal, a change of the target (Fig 3.2A) from an outline to a solid colour appeared 2000ms after the arm had been positioned. When movement was initiated and velocity exceeded 3.5cm/s, the cursor disappeared and only reappeared, showing the end position, when movement velocity reduced below 4cm/s without a subsequent increase over 7cm/s within 40ms. The arm was then moved back to the start position while feedback was displayed for 1000ms.

3.5. *Reaching performance*

3.5.1. *Healthy participants*

On day one and day five (pre- and post-training) reaching accuracy was established at four different movement times, 300, 500, 700 and 900ms, by performing blocks of 45 trials of a specific movement speed, presented in a random order. The reaches were performed at comfortable reaching speeds (500 and 700ms) (Soechting et al., 1995) as well as very fast (300ms) movement times and slow movements (900ms) (Nishikawa et al., 1999). The first five trials of each block were used for practice and to acquaintance with the target speed of the block and the subsequent 40 trials were analyzed. All four movement times were performed with targets at 0 and 45 degrees and the order of conditions was randomized. In all cases the aim was to end the movement as close as possible to the cross in the center of the target (Fig 3.2A).

Participants were instructed to perform the reach within a pre-determined movement time. The movement time was enforced by “dropping” the cursor at the hand position, that was achieved when the allowed movement time had passed, whether the hand had stopped moving or not. This cursor position was used for determining endpoint error. Any further corrective movement after this time did not influence the measurement. This arrangement means that movement times cannot be longer than the allowed time although shorter movement times are possible.

3.5.2. Stroke patients

Participants familiarized themselves with the task by performing one set of 15 reaches with continual visual feedback and one set without visual feedback at a variety of movement speeds. To set each individual's movement limits for testing and training individuals were encouraged to move as fast as possible in the 3rd set. The movement time needed for completion of the 4th fastest movement (80th percentile), for example 520ms, was used to set each individual's movement limit for the fastest movement speed *e.g.* 0-520ms. The limits for the other target speeds was then incrementally increased by 200ms which would make medium fast 520ms–720ms, medium slow 720ms-920ms and slow movement limit 920ms-1600ms in this example. In figures the target speeds are documented as slow=1, medium slow=2, medium fast=3 and fast=4. The average fast target speed for the individuals in the fast training groups was (570ms (+/- 160ms SD)) and for the slow group (545ms (+/- 110ms SD)). The average velocity for the 4 target speeds (1-slow, 2-medium slow, 3-medium fast, 4-fast) was thereby equally spaced with the greatest variability at the fast target speed (Table 3.1.)

Table 3.1. Velocity at set target speeds for the two training groups

Target Speed		Slow	Medium slow	Medium fast	Fast
Group	cm/s	Pre	Pre	Pre	Pre
Fast	mean	28.60	40.48	56.96	76.21
	sd	5.11	8.03	12.18	22.24
Slow	mean	29.43	36.80	55.71	80.27
	sd	7.35	8.71	11.14	23.97

On days 1 and 6 (pre- and post-training), reaching accuracy was established at these four set target speeds. All 4 target speeds were performed with targets at 0° (Fig 3.2A). The aim was to end the movement as close as possible to the cross in the center of the target while reaching at a specific movement speed. Individuals were told whether the expected movement speed was slow, medium slow, medium fast or fast. After each movement they either heard a pleasant sound which indicated a successful reach or a message appeared on the screen if the movement was 'Too fast' or 'Too

slow', indicating an unsuccessful trial. The order of target speed was determined by randomizing the first target speed by a Matlab® (Mathworks) script. Consecutive sets were performed at the adjoining target speed to the longest sequence (i.e. if starting with medium-slow (2) then order would be medium-fast(3), fast(4), slow(1) or if first would be fast(4) the order would be medium-fast(3), medium-slow(2), slow(1)). This procedure was followed to increase individual's ease of grading the movement speed to enable task performance. In each set the first five movements were used for practice and discarded before analysis. Consecutive reaches were performed to attempt to sample twenty successful trials, performed within the set movement limits, for each set target speed from a maximum of sixty trials per set (Fig 3.3).

The numbers of trials performed to achieve 20 successful repetitions of reaches (Fig 3.3) at the 4 set target speeds changed due to training indicated by an interaction ($F_{(3,102)}=5.477$, $p=0.002$) in a 3wrmANOVA TARGETSPEED(4)*TIME(2)*GROUP(2). Post-hoc analysis indicates that there was a significant reduction in trials required to reach criterion in the slow group for the slow $t_{(16)}=4.528$, $p<0.001$ and medium fast $t_{(16)}=2.691$, $p=0.016$ and for the fast group for the fast $t_{(18)}=2.214$, $p=0.040$ and related (medium fast $t_{(18)}=2.777$, $p=0.012$ and medium slow $t_{(18)}=2.368$, $p=0.029$) target speed. The change between the two groups is only significantly different at the slow movement speed $t_{(34)}=-3.393$, $p=0.002$.

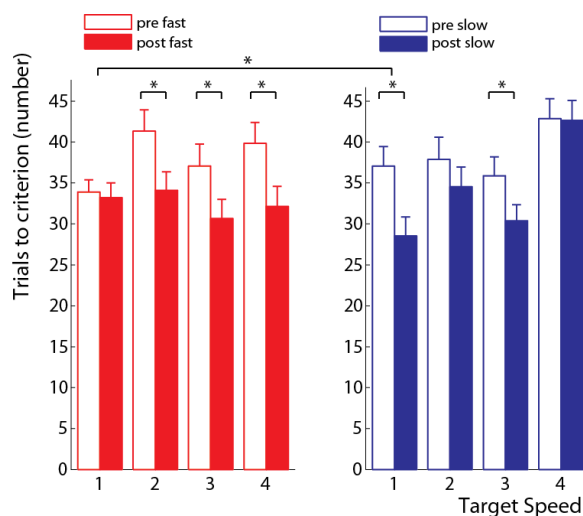


Figure 3.3 Trials to criterion. Group averages (red-fast, blue-slow movement speed training group) of number of trials required to reach 20 repetitions at the pre-determined movement speed. Measurements were taken at slow (1), medium slow (2), medium fast (3) and fast (4) target speed before(unfilled) and after (filled) training to determine the ability to perform accurate reaches at these different movement speeds.

3.6. Reaching training

3.6.1. Healthy participants:

On the second day, participants were randomly assigned to either a **fast** (cursor reappears after 300ms) or a **slow** (cursor reappears after 900ms) training group without stratification. They were instructed to what movement speed they had to train at (e.g. fast or slow) and during days 2, 3 and 4, trained to reach accurately at these movement times for 630 reaches per day (7 blocks of 90 repeats). Each training session lasted approximately 1 hour. During training the target size and location at 0 degrees remained unchanged but was now displayed as a bull's-eye (Fig 3.1 & Fig 3.2B, Training display) with concentric colored circles at 1, 2, 3, 4 and 5 cm radius. This provided feedback of results during training in order to maintain interest and incentivize participants. Points were awarded after every reach (5 points maximum when absolute error <1cm from the center of the target, 4 points for <2cm, 3 points for < 3cm, 2 points for < 4cm and 1 point for < 5cm error) and accumulated throughout the block, with a maximum score of 450 points per block. Participants were encouraged to increase their points per block and were reminded of their performance on the previous block and the previous day/s. Additionally; participants were informed that a monetary prize would be awarded to the participant demonstrating the greatest improvements due to training.

3.6.2. Stroke patients

On the second day, patients were randomized to either a fast or a slow training group. Randomization was stratified for age, Fugl-Meyer score and handedness. During days 2 – 5

individuals trained to reach accurately at the target movement speed, determined by their own fastest reaching ability (See Table 3.1 for averages), for 420 reaches per day (7 blocks of 60 repeats). Each training session lasted ~1 ½ h. During training, the target size and location at 0° remained unchanged but was now displayed as a bull's eye (Fig 3.1&3.2B, training display) with concentric colored circles at 1, 2, 3, 4, and 5cm radius. This provided feedback of results during training to maintain interest and incentivize individuals. Points were awarded after every reach (5 points maximum when absolute error < 1 cm from the center of the target, 4 points for <2-cm, 3 points for <3-cm, 2 points for <4-cm, and 1 point for <5-cm error) and accumulated throughout the block with a maximum score of 300 points per block. Movements that ended outside the target area and/or did not fall within the required training movement time were awarded 0 points and feedback of speed error was given. Participants were encouraged to increase their points per block and were reminded of their performance on the previous block and the previous day(s). Verbal encouragement was provided throughout and individuals were allowed to have rests in between sets as required.

3.7. Kinematic analysis

The kinematic measures I investigated were 1) endpoint error size and distribution, 2) movement speed and variance, 3) symmetry of velocity profiles and 4) the movement trajectories.

3.7.1. Endpoint accuracy

Our primary outcome measure was the reduction in endpoint error induced by training at the trained movement speeds (Fig 3.4A) and additional measures consisted changes in untrained speeds. Endpoint error is a valuable measure of performance to investigate individuals ability to perform a movement task as well as alterations in performing the task with repetition (Georgopoulos et al., 1981). The error on each trial was divided into a component along the movement direction (parallel error) (Fig 3.4B) and one orthogonal to the movement direction (perpendicular error; Fig 3.4C). Thus, the mean square Euclidean error (MSE) Fig 3.4A is equal to

$$MSE = \sum (Parallel\ error)^2 + \sum (Perpendicular\ error)^2$$

The change in endpoint error is depicted by actual pre- and post- error measures in centimeter but the improvement in performance is given in % change. Using this proportional method overcomes the difficulty of analyzing and interpreting improvement changes in individuals with varying abilities without over-weighting the effect in worse affected participants. The percentage change is a crude approximation however it does not encounter the difficulty of giving an average improvement, which is potentially above optimal performance in mildly affected individuals.

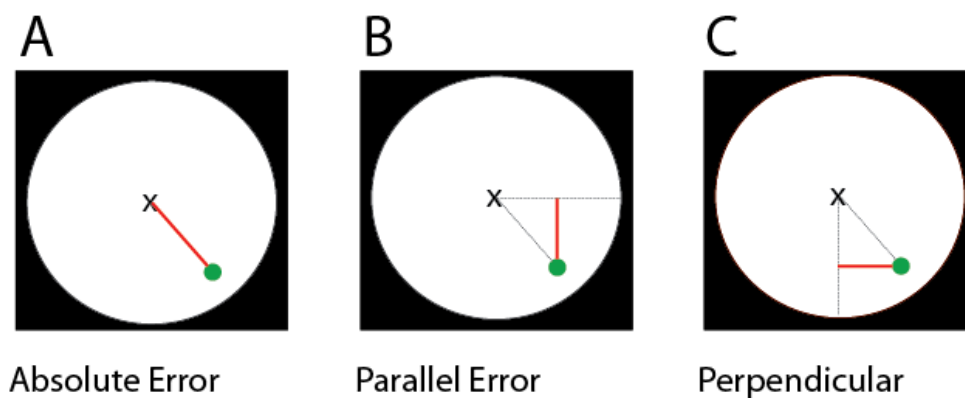


Figure 3.4. Determining endpoint error. Measures (red line) for determining endpoint accuracy of cursor (green dot) from the centre of the target (x). A) Root mean square error. B) Endpoint parallel error. C) Endpoint perpendicular error.

For inter-individual and inter-group comparison of data, the movements of individuals with left hemiplegia was mirrored along the sagittal plane and data are presented as right arm movements for all participants.

3.7.2. *Interpreting endpoint error*

To understand change in performance and the underlying mechanism and altered ability after training, the distribution of the endpoint error can be assessed in a variety of ways (Reynolds and Day, 2005).

The absolute error, or Euclidean error is the vector between the target center and the position of cursor presentation at the end of allocated movement time. For an endpoint error that is uniformly distributed around the target, as demonstrated for this representative subject (Fig 3.5A), a reduction in movement error will be detected by a reduction in the absolute error or Euclidean distance from the target centre. However if the errors are not uniformly distributed around the centre of the target, as demonstrated by data from another subject (Fig 3.5B), with a bias to end in a specific subspace of the work area (Fig 3.5C), the *absolute* error only provides limited information of the inaccuracy. Measuring the signed *constant* error (Fig 3.5C) as well as the spread around this error as the *variable* error (Fig 3.5D) is more sensitive and informative to interpreting change in individuals who experience physical difficulty in performing the task (Reynolds and Day, 2005, Schmidt and Lee, 2011).

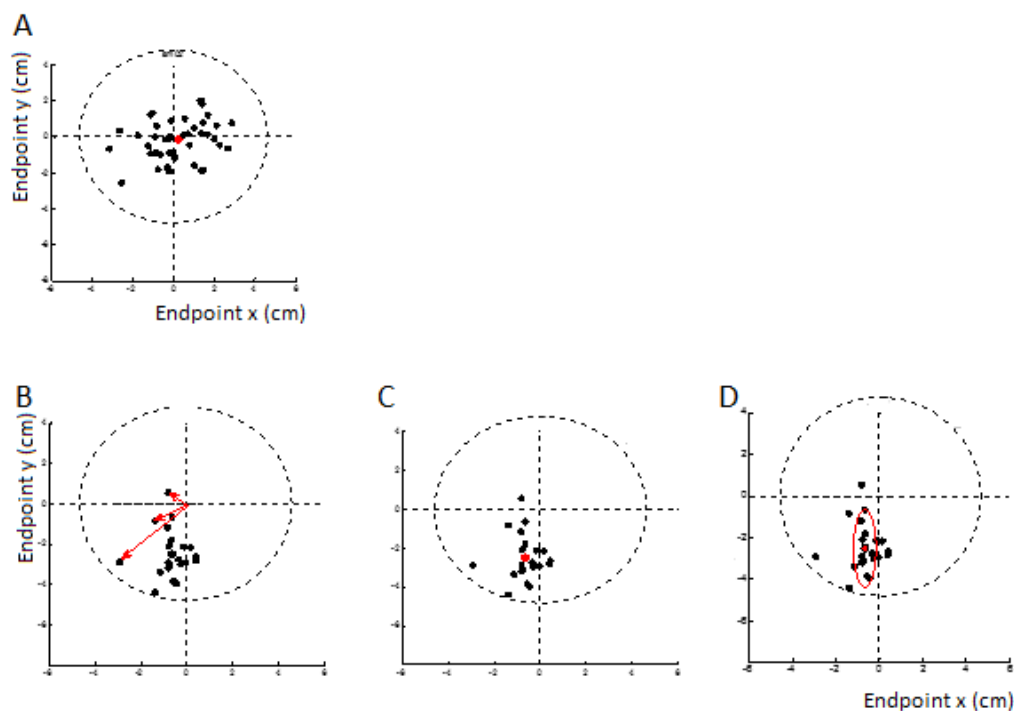


Figure 3.5. Demonstration of measures of endpoint accuracy for two individuals endpoint scatter in the target. A) Depiction of example data for endpoint error with distribution of scatter around centre of target. B-D) Depiction of example data with unequal endpoint scatter and resultant changes in endpoint analysis when depicting B) Absolute error measured as the average Euclidean distance from target centre to each endpoint position; C)

Constant error (bias), signed average endpoint error as a signed value; D) Variable error, average x and y spread of the endpoints around the Constant error.

3.7.3. *Maximum movement speed and variance*

The maximum movement speed and standard deviation of this speed was determined on a trial-by-trial basis and averaged for each individual for each set target speed. This measure was used to investigate movement performance at the 4 set target speeds and changes induced to these measures due to the two training protocols.

3.7.4. *Symmetry of velocity profiles*

In stroke patients, movement performance in this task differed between individuals. The variability stemmed from their clinical impairment and therefore the ability to perform the reaching task. The length of reaches was not the same between individuals and within individuals and plotting the velocity against a scalar distance measure would make interpretation difficult. I therefore normalized the reaching length on a trial-by-trial basis to the reach extent by interpolation. The velocity is therefore plotted against the percentage of the reach length. Thereby comparison between individuals with varying movement ability is possible. Reaching length differed between patients and some patients demonstrated a consistent undershoot.

Changes to the velocity in relation to the extent of the reach (%) were used to analyze the timing of the maximum movement speed and changes, induced by the two training protocols.

3.7.5. *Movement trajectories*

The movement trajectory and specifically the directness of the movement path were investigated in stroke patients. Directness of movement was established as a ratio between the direct path from start to endpoint with a sample-by-sample sum of the x- and y-axis coordinates and is presented as a percentage of the direct path.

3.8. EMG

See chapter 7.2.

3.9. TMS

See chapter 6.2.

3.10. Data Analysis

IBM SPSS software and custom written Matlab® (Mathworks) routines were used for data analysis. The alpha level of $p \leq 0.05$ was used to determine statistical significance.

Normality of data distribution was confirmed with the Kolmogorov-Smirnov test. Repeated measures ANOVA's were performed and when the Mauchly test indicated that the assumption of sphericity was violated, a Greenhouse-Geisser correction was used. Post hoc Student's t-test were performed when the ANOVA indicated significant differences in the data. For non-parametric parameters like the Fugl Meyer Upper Extremity Subset and spasticity measured by the MAS the Wilcoxon Signed rank test was used to analyze repeated measures, i.e. changes due to training and the Mann-Whitney U Test to establish differences between independent samples, i.e. between groups.

In the training phase repeated-measures analysis of variance (rmANOVA) were used to investigate the BLOCK(7)*DAY(4)*GROUP(2) interaction. Changes within a training day were investigated as a measure of learning and changes between training days as a measure of retention using rmANOVA as DAY(4)*GROUP(2) and DAY(3)*GROUP(2) interactions respectively (Reis et al., 2009).

$$learning = \sum_{i=1}^4 \frac{Error(Block(first)day_i)}{Error(Block(last)day_i)} / day_i$$

$$retention = \sum_{i=1}^3 \frac{Error(Block(last)day_i)}{Error(Block(first)day_{i+1})} / day_i$$

In the testing phase repeated measures ANOVA investigated the TIME(2)*TARGET SPEED(4)*GROUP(2) interaction for changes in error and movement speed variability at the trained and non-trained movement speed. Further analysis investigated kinematic changes for between group differences.

To investigate correlations between findings I performed Spearman's and Pearson's correlations, for non-parametric and parametric data respectively, on a subject-by-subject basis and findings are expressed by the rho or r-value as well as the level of significance.

4. Movement speed is biased by prior experience

The work described here has been previously published:

Hammerbeck U, Yousif N, Greenwood R, Rothwell JC, Diedrichsen J. Movement speed is biased by prior experience. *J Neurophysiol* 2014; 111(1): 128-133

4.1. Introduction

This pilot trial was performed to investigate the amount of learning observed in an intensive upper limb reaching paradigm in young healthy individuals before using the protocol for the main experiment in stroke subjects. Over three consecutive days, a group of healthy young volunteers practised a 20cm centre-out arm reaching task; half of them were trained to move fast whereas the others were trained to move slowly. A day before and a day after the training sessions, participants were required to make reaching movements within 4 different time windows. One of these was the same as the trained task; the 3 others were different. Endpoint accuracy and kinematic variables were measured to plot a speed-accuracy trade-off for performance at the 4 probed movement speeds. Learning was defined as improved endpoint accuracy as well as a reduction of the variability of kinematic measures during task performance. Training speed specific improvements as well as generalisation of improved performance to non-trained speeds were investigated.

This protocol can establish a baseline measure of a speed accuracy trade-off function for these reaching tasks and is sensitive to change. At the end of training, people in both training groups made more accurate movements at less variable speeds for the speed that they were trained at. Improvements were also seen at similar speeds as trained but did not generalise broadly to all movement speeds. The changes in movement performance generalized to other movement directions, indicating that the underlying adjustment is relatively global.

Interestingly I found that this came at the cost of biasing the speed in the untrained movements. Those who had been trained to move slowly tended to move slower than before training, whereas those who had been trained to move fast did the opposite. Theoretical models propose that the motor system chooses a speed that optimizes a cost function (Todorov and Jordan, 2002) representing a combination of the importance or reward value of the goal (Xu-Wilson et al., 2009), the energy required to execute the movement (Mazzoni et al., 2007) and the cost of the wait (Tanaka et al., 2006; Shadmehr, 2010; Shadmehr et al., 2010; Haith et al., 2012). For example, speed

of walking with an arthritic hip could be a compromise between reaching the goal of catching the bus, and minimising pain. This result however indicates that additionally movement speed is also habitual in that a certain speed is chosen because recent movements have tuned the system to this trained speed.

We hypothesised that training at fast and slow movement speeds would demonstrate different learning mechanisms and generalisation to non-trained movement speed. Because we hypothesised that training at fast movement speed would be more difficult we assumed that this training would result in widely generalised improvements in accuracy, to movement speeds that were easier to perform, whereas improvements due to slow training would be more training speed specific.

4.2. *Methods*

See general Methods Chapter 3.

4.3. Results

The protocol was performed in a group of 18 healthy, right handed participants (mean age: 28.94, SD 8.07, gender; 11 female).

4.3.1. Speed choice during pre-test

The constraint on movement speed I imposed for the 4 different target speeds was asymmetrical as can be observed (Fig 4.1) by the limited spread of data at the fastest speed and much greater variance at low target speeds. The choice of target speed differed however between subjects and this choice was relatively stable demonstrated by the subject-by-subject correlation between the slowest target speed and the other slow target speed conditions (900 -700, $r_{(16)}=0.894$, $p<0.001$; 900-500, $r_{(16)}=0.868$, $p<0.001$). Because the constraint of moving very fast in the 300ms condition prevents a true choice of speed I observe that the effect of the prior is abolished (900-300, $r_{(16)}=0.261$, $p=0.295$).

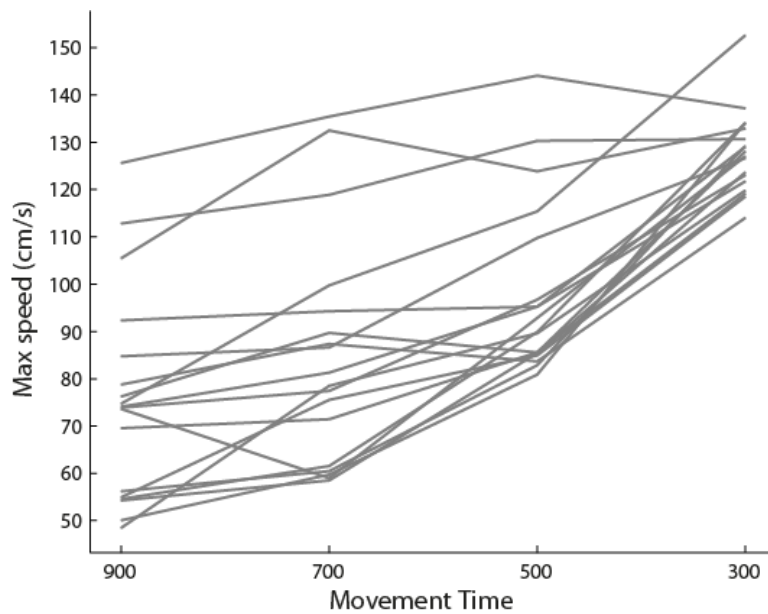


Figure 4.1. Individual preferred movement speed at the 4 set movement time before training

4.3.2. *Movement changes during training*

Over the three days of training, participants reduced the variability of peak movement speed (Fig 4.2B). A two-way rmANOVA on the standard-deviation of the maximal speed from the first to the third day, with the factors GROUP (fast vs. slow) and TIME (first vs. third training day) showed a significant effect of TIME ($F_{(1,16)} = 53.451, <0.001$). Simultaneously, participants also showed a significant improvement of their movement error (Fig 4.2C; $F_{(1,16)} = 34.708, p < 0.001$) in the same type of rmANOVA which was similar in the slow and fast training group.

For the fast group, the maximum movement speed remained relatively constant over the 3 days (Fig 4.2D), whereas it decreased slightly in the slow group, resulting in a significant effect of GROUP ($F_{(1,16)} = 75.976, p < 0.001$) and a TIME x GROUP interaction ($F_{(1,16)} = 5.762, p = 0.029$) and a marginally significant effect of TIME ($F_{(1,8)} = 5.021, p = 0.055$). This is probably because the slow group moved at their preferred speed at the beginning of training and waited at the end of the movement for the reappearance of the cursor. Over the training days they abandoned this “move and wait” strategy and slowed down their movements. This strategy was not available to the fast group who were moving at close to their maximum speed anyway.

The interval between the onset of each movement was matched between conditions. Since the percentage of correct movements did not differ, the average rate of reward during the training phase was the same in each groups (Table 4.1).

Table 4.1. *Statistical summary comparing reward rate during training between the fast and slow training group*

Reward rate	Mean (+/- SE)		Significance
	Fast	Slow	
Percentage correct	93.4% (0.68)	93.32% (1.10)	$t(16) = 0.075, p = 0.941$
Trial Duration (ms)	2663.9ms (19.7)	2747.8ms (55.5)	$t(16) = -1.426, p = 0.173$
Reward rate	1.75/sec (0.02)	1.70/sec (0.05)	$t(16) = 1.010, p = 0.328$

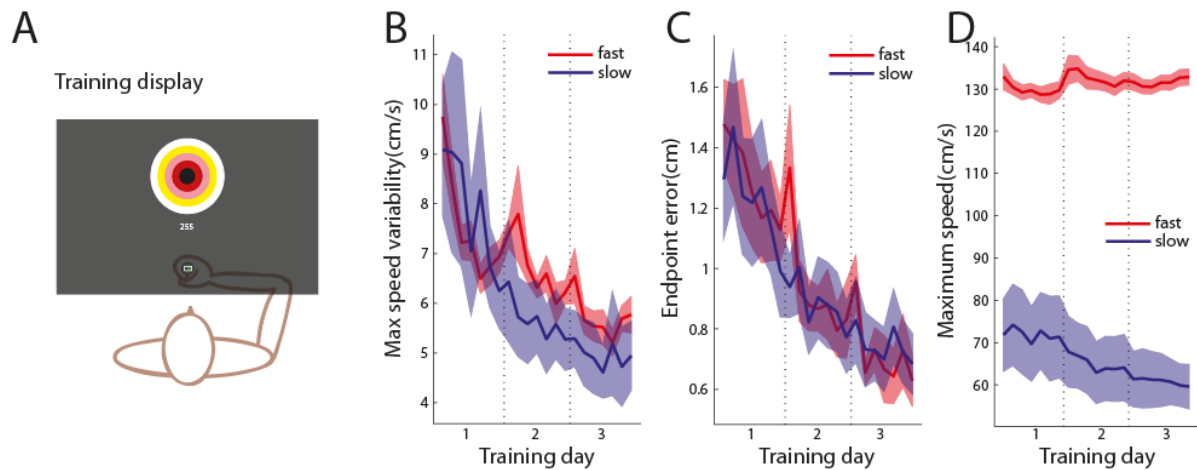


Figure 4.2. Reaching performance during training days (Day 2-4). A) Diagram of experiment with target placed 25cm directly in front of participants, and bulls-eye scoring system. B-D) show how performance in the training blocks (9 per day) changes over the three days in the fast (red) and slow (blue) training group. B) Variability (SD) of peak movement speed; C) root mean square endpoint error; and D) mean peak movement speed.

4.3.3. Influence of training on movement speed

Before and after the three days of training, performance was tested at 4 different speeds by changing the time at which the cursor reappeared (300, 500, 700, 900 ms). Fig 4.3A and 4.3B shows that participants adapted peak velocity to match the time available for moving.

By the end of training, participants had developed a bias towards the trained speed. The fast group (Fig 4.3A) moved quicker at all speeds except the highest movement speed, where faster movements were difficult. The slow group (Fig 4.3B) moved more slowly at all speeds except the highest movement speed where lower movement speeds would lead to task failure. This was confirmed in a two-way rmANOVA on the change in movement speed (Fig 4.3C) from pre- to post-test. There was no significant difference of movement speed before training between the groups. There was a significant main effect of TRAINING GROUP (slow vs. fast) ($F_{(1, 16)}=9.597$; $p<0.007$), as well as a significant GROUP x TARGET SPEED interaction ($F_{(1.932, 30.91)}=3.415$; $p=0.047$). This interaction was not driven by the significant changes that are seen at the trained movement speed as a 2x2

rmANOVA for the untrained movements speed (500ms and 700ms) also yielded a significant GROUP x TARGET SPEED interaction ($F_{(1,16)}=11.172$; $p=0.004$) as well as a significant effect of GROUP ($F_{(1,16)}=1.436$; $p=0.011$).

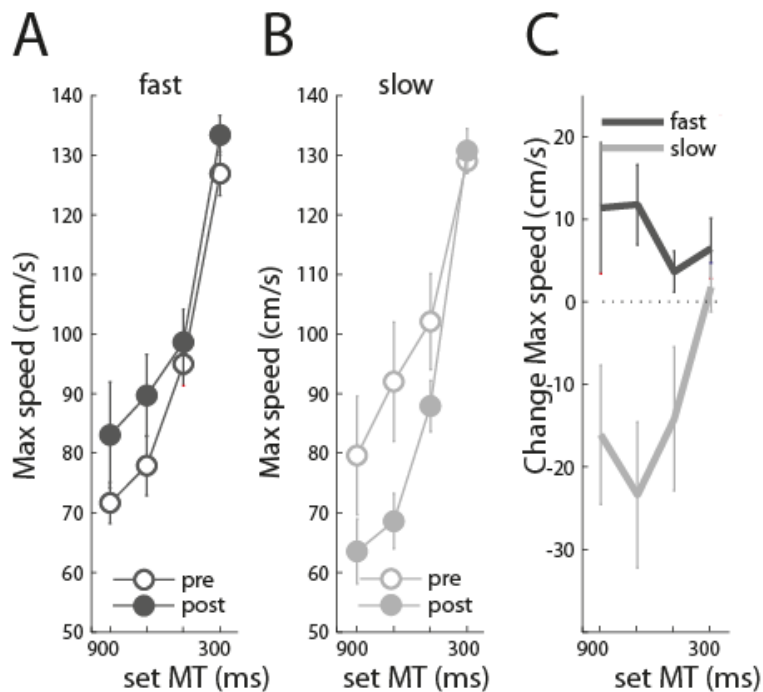


Figure 4.3. Comparison of changes in maximum movement speed A-C) due to training. A) data from the fast training group before (unfilled) and after (filled) training for movement times of 900, 700, 500 and 300ms. B) slow training group measures. Plot C) plots pre-post change scores of maximum speed.

Training did not only alter peak velocity, but also the velocity profile of the movement (Fig 4.4). The profiles for the slowest movement times were highly skewed before training demonstrating that participants moved and then waited for the end of the movement time at the target. Training at the slow speed led to more symmetric velocity profiles by delaying the time of peak speed (Fig 4.4E-H). This was not the case for the group that trained at the fast speed (Fig 4.4A-D). The time at which peak speed was reached exhibited a significant GROUP x TARGET SPEED interaction ($F_{(3,24)}=7.460$, $p=0.001$), as well as a significant effect of GROUP ($F_{(1,16)}=8.026$, $p=0.012$).

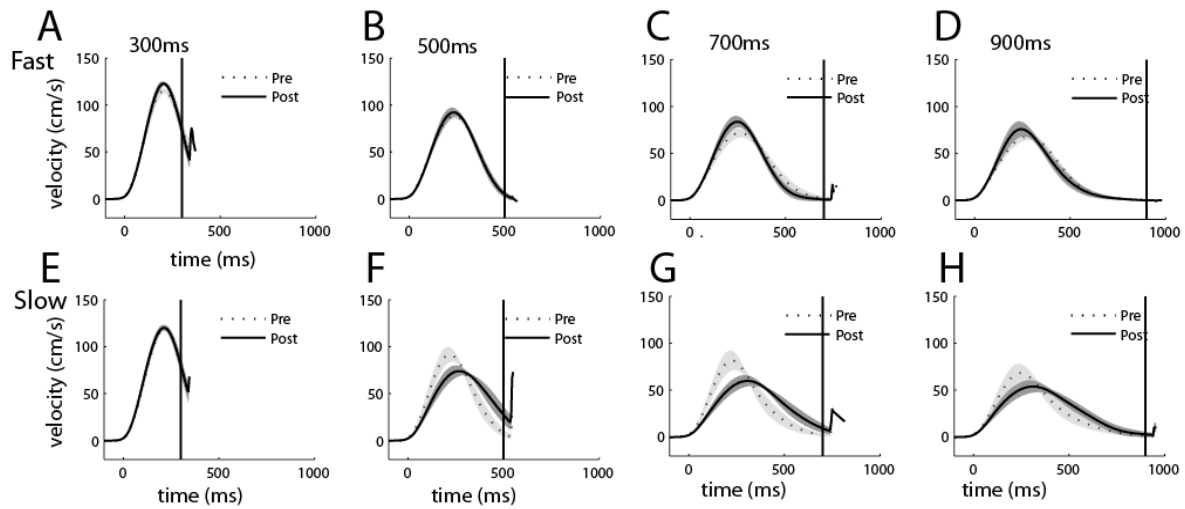


Figure 4.4. Changes to velocity profiles induced by training. Group average (\pm SD of individuals) of: A-D) fast and E-H) slow group at 300ms: A+E, 500ms: B+F, 700ms: C+G and 900ms: D+H.

Reduced variability of peak speed observed during training (Fig 4.2C) was also evident when inspecting the pre- and post-training performance. Interestingly, the reduction was specific to the trained speed. The fast training group reduced the variability of movement speed mostly for the higher speeds (Fig 4.5A), whereas the slow group decreased it mostly for the lower speeds (Fig 4.5B). Despite the apparent difference for the level of speed variability prior to training, these differences did not reach statistical significance in a 2wrmanOVA (MT(4)*Group(2)). This training-specific effect can be seen most clearly in the pre- to post-test difference plots (Fig 4.5C). A 2 factor rmANOVA confirmed that there was a highly significant GROUP x SPEED interaction ($F_{(3,48)}=5.047$, $p=0.004$). Between group, post-hoc t-tests on the reduction of movement speed variability was significantly changed for the fast training group ($t_{(16)}=-2.570$; $p=0.021$) and showed a trend for the slow group ($t_{(16)}=-2.037$; $p=0.059$). The combination of a training-dependent movement speed bias and a specific reduction in speed variability suggests a similar mechanisms as has been observed for training induced changes in movement direction (Verstynen and Sabes, 2011).

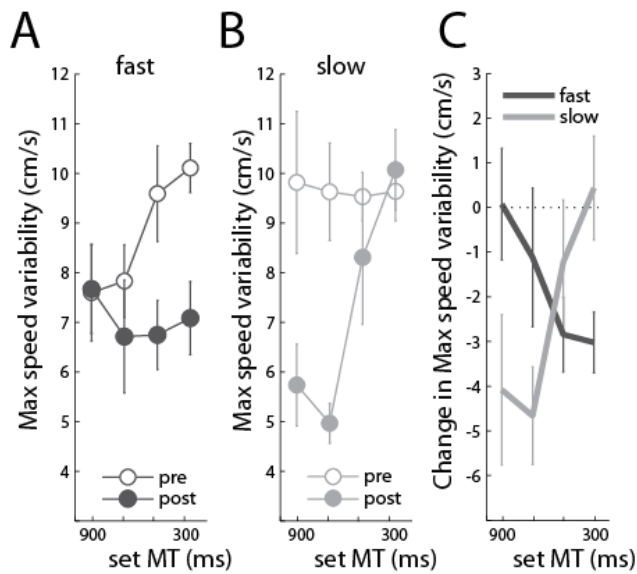


Figure 4.5. Comparison of changes in maximum speed variability due to training. A) data from the fast training group before (unfilled) and after (filled) training for movement times of 900, 700, 500 and 300ms. B) slow training group measures. Plot C) plots pre-post change scores of maximum speed variability.

4.3.4. *Endpoint accuracy*

Movement accuracy improved with training. When separated into parallel and perpendicular components, I found that parallel error (Fig 4.7 B,C,E) decreased, particularly for the fastest movements in the fast group (Fig 4.7B). An rmANOVA on the pre-post differences (Fig 4.7D) confirmed a significant TRAINING GROUP x TARGET SPEED interaction ($F_{(3,48)}=9.164$, $p=0.001$) with a post-hoc t-test showing that the improvement was significantly greater in the fast than the slow group for the fastest target speeds ($t_{(16)}=-2.739$; $p=0.013$). For the shortest movement duration, the parallel error correlated strongly with the movement speed on a trial-by-trial basis (Fig 4.6), such that slow movement undershot and fast movement overshot the target ($r = 0.795$, ± 0.061 (SEM)). Therefore reductions in speed variability would automatically lead to reduced parallel error. Indeed, on a subject-by-subject level, reductions in the variability of the parallel error were significant correlated with the reduction in peak speed variability ($r_{(16)}=0.649$, $p=0.004$) Fig 4.6).

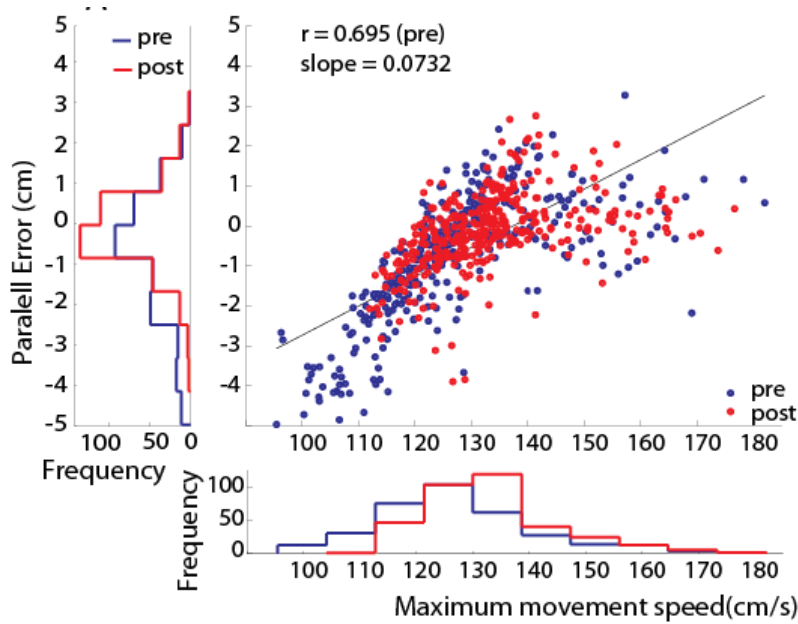


Figure 4.6. Correlation of maximal movement speed for each reaching movement and corresponding under- or overshoot before (blue) or after (red) training at fast movement speed. Additionally frequency of maximum movement speed and parallel error range is depicted and how this changes with training.

Perpendicular error was also reduced after training in both groups (Fig 4.7E-F) demonstrated by a significant effect of TIME in two-way rmANOVAs on the pre-post data ($F_{(1,16)}=58.099$, $p<0.001$).

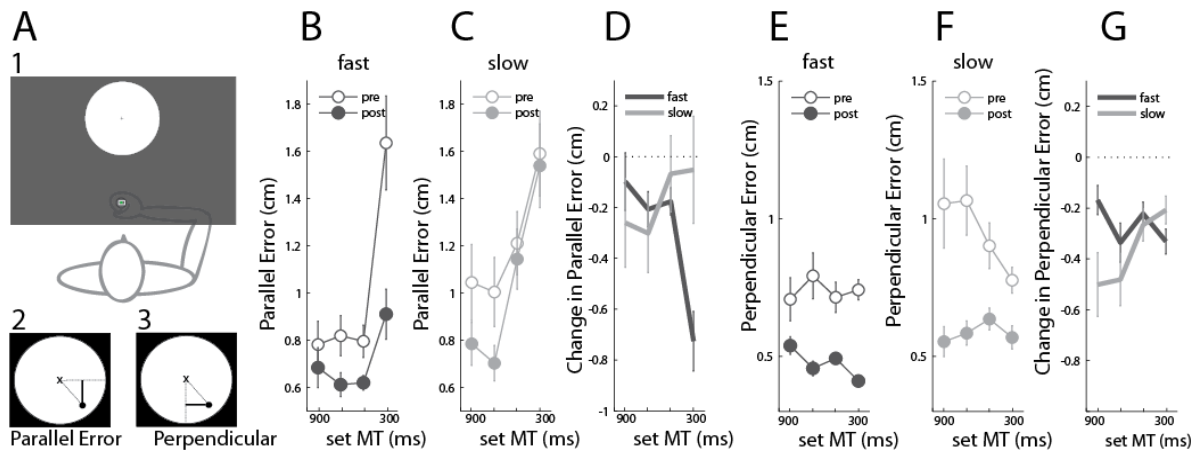


Figure 4.7. Reaching accuracy changes after training. A1) Experimental display during pre- and post-testing. A2-3) Determining parallel and perpendicular Error. B-D) Measures of parallel error and E-G) perpendicular error at each of the 4 movement times before (unfilled) and after (filled) training. B&C) parallel error for the fast and slow training groups respectively; E&F) perpendicular error for the fast and slow training groups. D&G) pre-post difference scores in parallel and perpendicular error.

The improvement was particularly evident in the slow training group when moving at the longest movement times ($t_{(8)}=-2.836$; $p=0.022$). The latter was confirmed by a two-way rmANOVA on the pre-post training change (Fig 4.7G) showing a TRAINING GROUP x TARGET SPEED interaction ($F_{(1.798, 28.762)}=4.158$, $p=0.030$).

4.3.5. ***Generalisation to another movement direction***

Finally, I assessed how training changed preferred speed and endpoint accuracy for movements aimed at a target that was 45 degrees clockwise to the trained direction (Fig 4.8A). Figure 8B shows that, compared with the baseline (pre-training) data, movements at all target speeds were slower in the slow training group and faster in the fast training group with a significant effect of TRAINING GROUP ($F_{(1,16)}= 11.391$, $p= 0.004$). Peak speed variability was also reduced in the new direction (significant effect of TIME, $F_{(1,16)}=8.664$, $p=0.010$), but to a lesser degree than in the trained direction (Fig 4.8C).

Analysis of the parallel component of the error (Fig 4.8D) demonstrated an effect of GROUP ($F_{(1,16)}=4.227$, $p=0.056$). The fast group significantly improved their parallel error at the fast movement speed (post-hoc t-test: $t_{(16)}=-2.492$; $p=0.024$). In contrast, the perpendicular error (Fig 4.8E) showed only small, non-significant improvement for both groups, suggesting that the acquired improvement in perpendicular accuracy was specific to the trained movement direction.

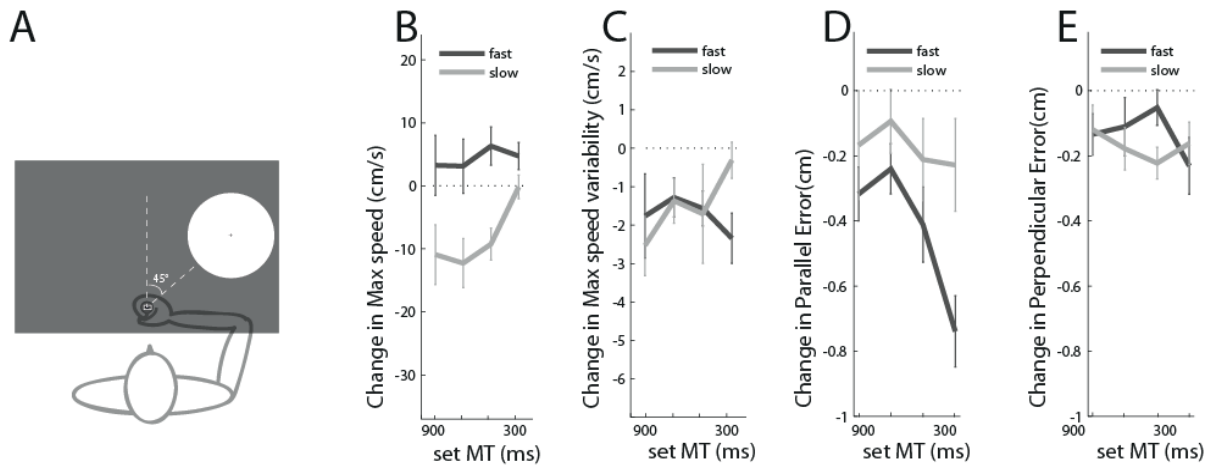


Figure 4.8. Transfer of performance to a target rotated 45 degrees clockwise (A). B) pre-post change in maximum movement speed in the fast (red) and slow (blue) training groups; C) endpoint error; D) perpendicular error; and E) parallel error.

4.4. Discussion

In experiment 1 I explored whether a protocol of intensive reaching practice in a robotic manipulandum was able to demonstrate skill learning. Training was delivered either with an emphasis on high or low movement velocity and the effect of this training on training-speed-specific reaching and generalisation to other non-trained speeds was investigated. I piloted this protocol in healthy individuals before using it in stroke subjects, where repetitive reaching training would be functionally beneficial and relevant. The improvement in endpoint accuracy as well as the reduction in kinematic variability demonstrated, that this training was able to induce learning detectable in speed-accuracy trade-off plots. However, I made an unexpected interesting finding that training speed influenced the choice of movement speed in consecutive reaches.

The present results suggest that the speed with which people move is not solely determined by an optimality criterion that combines task constraints, the reward value of the target, and intrinsic costs of movement (Todorov and Jordan, 2002). Instead, the choice of movement speed is partly habitual, depending on prior experience and modifiable through prolonged training at a specific speed. The experiments used a standard centre-out reaching task, in which movement speed was asymmetrically constrained: the cursor indicating hand position was removed at the start of movement and was redisplayed after 300-900ms as a stationary cursor that indicated the end point. If the cursor appeared, for example after 500ms, then movements that were too slow and had not reached the target by that time would be penalised for undershooting. However, maximum speed was not specified. Fast movements arrive early at the end point, and the only consequence is that participants have to wait a short time before the cursor reappears. Thus, this method effectively enforces a minimum movement speed, while leaving participants free to choose as fast a speed as they are comfortable with. This redundancy allowed me to measure the influence of the preferred (or habitual) movement speed. While I could have also used a task in which I simply asked people to move at their preferred speed in the absence of any constraints, such experiments can be highly

susceptible to influences of task instructions. I therefore used this partly-constrained version, which also allowed me to test the influence of an acquired habitual speed across different speed constraints.

After training, participants were tested at movement speeds that had not been trained. I observed that their preferred speed was altered: the fast training group moved faster and the slow training group slower. This change was also evident in the velocity profiles demonstrating a change in maximum speed as well as an alteration of the time of this speed (Flash and Hogan, 1985). Simultaneously, each group showed a marked reduction in the trial-by-trial variability of peak speed when tested at their trained movement speed. I suggest that this effect is a consequence of use-dependent learning in which the movement speed that enhances success during training, biases the speed of subsequent movements (Georgopoulos et al., 1981). In essence, my experiment constitutes a temporal version of the spatial phenomenon described by Verstynen and Sabes (2011), who found that moving repeatedly to a single target reduced the directional variability to the trained target, but also biased the direction of movements to nearby targets. In the experiments of Verstynen and Sabes (2011), the spatial effects occurred rather rapidly within a single experimental session. In the present case, I was interested in lasting long-term consequences of training, and did not examine how the effect changed during the training days. Nevertheless, the effects were consolidated and still present one day after the final training session.

The bias towards the practised speed of movement transferred to a different movement direction. While I did not assess how far this changed preference would generalize (i.e. to different movement with the same effector, movements with the other hand, or with other body parts), my results suggest that habitual movement speed is influenced by training on a more global level than visuo-motor adaptation (Krakauer et al., 2006) or changes in proprioceptive accuracy (Ostry et al., 2010).

An unresolved question concerns the exact nature of the change in preferred movement speed. I have here favoured the idea that training generates an attractor that biases movements towards the speed at which the training was performed in the same way as repeatedly practising movements in one direction biases subsequent movements towards the same direction (Verstynen and Sabes, 2011). However, it is also possible that training at different speeds influences movement vigour in general (Haith et al., 2012). Because I trained participants only on the slowest and fastest condition of the tested range, the data on speed biases does not allow me to differentiate between these two explanations. However, an attractor-like mechanism can simultaneously account for the specific reduction in the movement speed variability, as it would predict that movement speeds nearer to the trained velocity would be pulled towards the learned prior. It is unclear how a general change in movement vigour would account for this result.

Another important question is whether the change in the preferred movement speed was induced solely by the act of moving at this speed (Diedrichsen et al., 2010, Verstynen and Sabes, 2011), or whether the experience of successful movements at that particular speed was critical (Huang et al., 2011). Further experiments are required to tease apart the role of these two factors.

Nonetheless, my finding provides a new and important insight into how the motor system determines movement speed for any given task. All previous models share the common assumption that the chosen speed is a moment-by-moment compromise between external and internal constraints. For example, in the model by Tanaka et al (Tanaka et al., 2006), movement duration is set as low as possible while still fulfilling the accuracy constraints: faster movements would entail more signal dependent noise and reduce accuracy. An external factor that speeds up movement times is the reward value of the goal. Experiments in the macaque show that eye movement speed can be more than 20% higher when the target is rewarded compared to non-rewarded (Bendiksby and Platt, 2006). Similar results have been described in humans (Shadmehr et al., 2010). Most recent models combine these factors by proposing that the motor system strives to maximize the overall

rate of reward, which leads to a compromise between the probability of success and a hyperbolic discounted reward value (Shadmehr et al., 2010, Haith et al., 2012). These type of models cannot account for these results, as the reward probability (i.e. success rate), as well as the rate of reward (Haith et al., 2012) was matched across the two training groups.

This experiment demonstrates that the speed we move at is also influenced by past experience. It indicates that the motor system does not approach each task as a blank slate and re-optimizes the preferred movement speed de novo, but rather carries with it preferences for certain speeds of movement. The existence of such a preference, even at the start of training, could be observed in the slow training group, which moved faster than necessary, and therefore had to wait at the goal. Our results also demonstrate that this natural preferred movement speed can be modified through repeated practice at an enforced speed.

This insight may also have important implications for understanding and treating clinical movement disorders. Slowness of movement is a common feature but is also observed in healthy ageing (Gill et al., 1997, Mazzoni et al., 2007). These changes are often explained as an optimal response to a changed speed-accuracy trade-off, i.e., the movement may be slowed down to be able to achieve the necessary level of spatial accuracy required by every-day task. Alternatively, slowness of movement may be consequence of a changed reward to effort or cost ratio (Mazzoni et al., 2007). Our findings suggest that, while the initial slowing may be indeed caused by a combination of these factors, the slowness may be further consolidated by the habitual formation of a behavioural bias that slows down all movement. Thus, even if the underlying deficit was removed, slowness of movement may persist due to a persistent change in the preferred movement speed. Following this idea, it may not be enough to improve accuracy of movement through physical therapy; it may also be necessary to overcome the habitual slow movement speed by training at speeds that are higher than the preferred set point.

I also found practice-related improvements in movement accuracy. Part of this was linked to reduced variability of maximal movement speed: this was apparent especially for the parallel error (parallel to the target direction) for the fast training group, in which the reduced error almost fully accounted for the reduced variability in peak velocity. Gains in perpendicular accuracy were more specific to the trained movement direction. This indicates that the accuracy gains may depend on learning the muscle and joint dynamics for a specific movement direction, leading to relatively narrow generalization (Orban de Xivry et al., 2011).

Our experiment demonstrates that prior training influences the chosen movement speed, even under relatively constrained conditions. The effects were visible even one day after the last training day and generalized to a different movement direction. Although these findings imply general and long-lasting changes to preferred speed, I have not yet established whether these effects generalize outside of the experimental setting, and over what time period they disappear after the end of training. Nonetheless, our findings demonstrate that the motor system re-optimizes the movement speed for any given task by taking into account a strong internal prior that is shaped by recent experience.

*5. Learning at slow and at
fast movement speed in
stroke*

5.1. Introduction

Individuals affected by stroke move more slowly (DeJong et al., 2011) although movements in daily life need to be performed at a variety of speed and accuracy requirements (Fitts, 1954). Slow movement during rehabilitation could reinforce this slowness by use-dependent learning mechanisms as observed in healthy individuals (Diedrichsen et al., 2010, Hammerbeck et al., 2014). Training protocols for the more severely affected stroke patient have historically been performed at slow movement speed, probably at least partly due to the fear that fast movements could increase spasticity, a velocity dependent increase in tonic stretch reflexes (Lance, 1980). Spasticity has traditionally been thought to reduce the quality of movement (Bobath, 1990). Yet we know that stroke patients are able to move faster and in some respects (kinematics) their movements can actually be smoother when moving fast (DeJong et al., 2011). In addition moving fast can increase the amount of force required during training sessions, and thereby increase muscle activity during therapeutic interventions (DeJong et al., 2011). How training at different movement velocities influences motor learning in stroke patients has however not been mechanistically investigated.

In this trial the effectiveness of fast versus slow training of arm reaching movements was compared in chronic stroke patients. The task was highly constrained so that improvement could only occur through better task performance using the affected upper limb rather than utilisation of compensatory strategies. Outcome was measured in terms of reaching accuracy at trained and non-trained movement speeds as well as more general measures of arm function. I also investigated whether there was any relationship between pre-training clinical scores and the amount of improvement.

I hypothesised that individuals affected by stroke would be able to improve reaching accuracy when training at slow and fast movement speeds. I further was interested to investigate if differential learning mechanisms were used to improve performance at the two movement speeds.

5.2. Methods/Study Design

5.2.1. Participants

See chapter 3.1 for full detail

5.2.2. Material

See chapter 3 for full details of Methods.

Although determining the endpoint error in the un-constrained fashion explained in chapter four led to interesting findings about the influence of repetition at a specific movement speed on the habitual speed in consecutive movements, I changed the paradigm before recruiting stroke subjects. In the experiment in chapter 4 individuals training at high velocity performed near ballistic movements and optimized the timing of when they arrived at the target. This is not how functional reaching tasks are performed and this training would have limited functional benefit after stroke. I therefore altered how I determined the movement endpoint. I constrained movement time so that individuals had to stop moving within a specific movement time. Movement accuracy was measured once movement velocity had dropped below 4cm/s without a consecutive rise over 7cm/s in endpoint correction in the consecutive 40ms. To test whether individuals still showed the same learning in this slightly altered paradigm I performed another set of experiments in a group of 14 healthy right handed individuals (age; mean: 22.86, SD +/- 3.29, gender; 4 female) attending for 5 consecutive days .

5.3. Results

5.3.1. Control experiment and comparison with previous experimnt

In this new paradigm, training-speed-specific improvements were observed for the fast and the slow training group (Fig 5.1 A-C) as well as generalisation of accuracy improvements to other movement speeds (3wrmANOVA TargetSpeed(4)*TIME(2)*GROUP(2); there was no interaction but an effect of TIME $F_{(1,12)} = 15.503$; $p=0.002$).

The maximum movement speed variability, another measure employed to observe learning, also reduced after training for both training groups (Fig 5.1 F-H) by an effect of TIME ($F_{(1,12)} = 15.691$; $p=0.002$) in a 3wrmANOVA TargetSpeed(4)*TIME(2)*GROUP(2). This reduction was different at the various target speeds (Effect of TargetSpeed ($F_{(3,36)} = 72.079$; $p \leq 0.001$) but did not demonstrate an interaction.

To compare if this effect is similar to the learning observed in the previous protocol the improvements were expressed as percentage change (Fig 5.1 D&I)) because an interaction indicated that the baseline error was not the same for the two experiments (Fig. 4.6 and 5.1) for endpoint error 2wrmANOVA (Experiment(2)*TargetSpeed(4) by an interaction ($F_{(3,90)} = 5.156$; $p=0.002$) as well as for movement speed variability (Fig. 4.5 and 5.1) ($F_{(3,90)} = 11.018$; $p=0.002$).

When comparing the percentage change of endpoint error (Fig 5.1 D&E) between the two protocols with a 2wrmANOVA(EXPERIMENT(2)*TARGETSPEED(4)), neither the fast training group ($F_{(1.63,22.815)} = 2.676$; $p=0.099$) nor the slow training group ($F_{(3,39)} = 1.160$; $p=0.337$) showed an interaction.

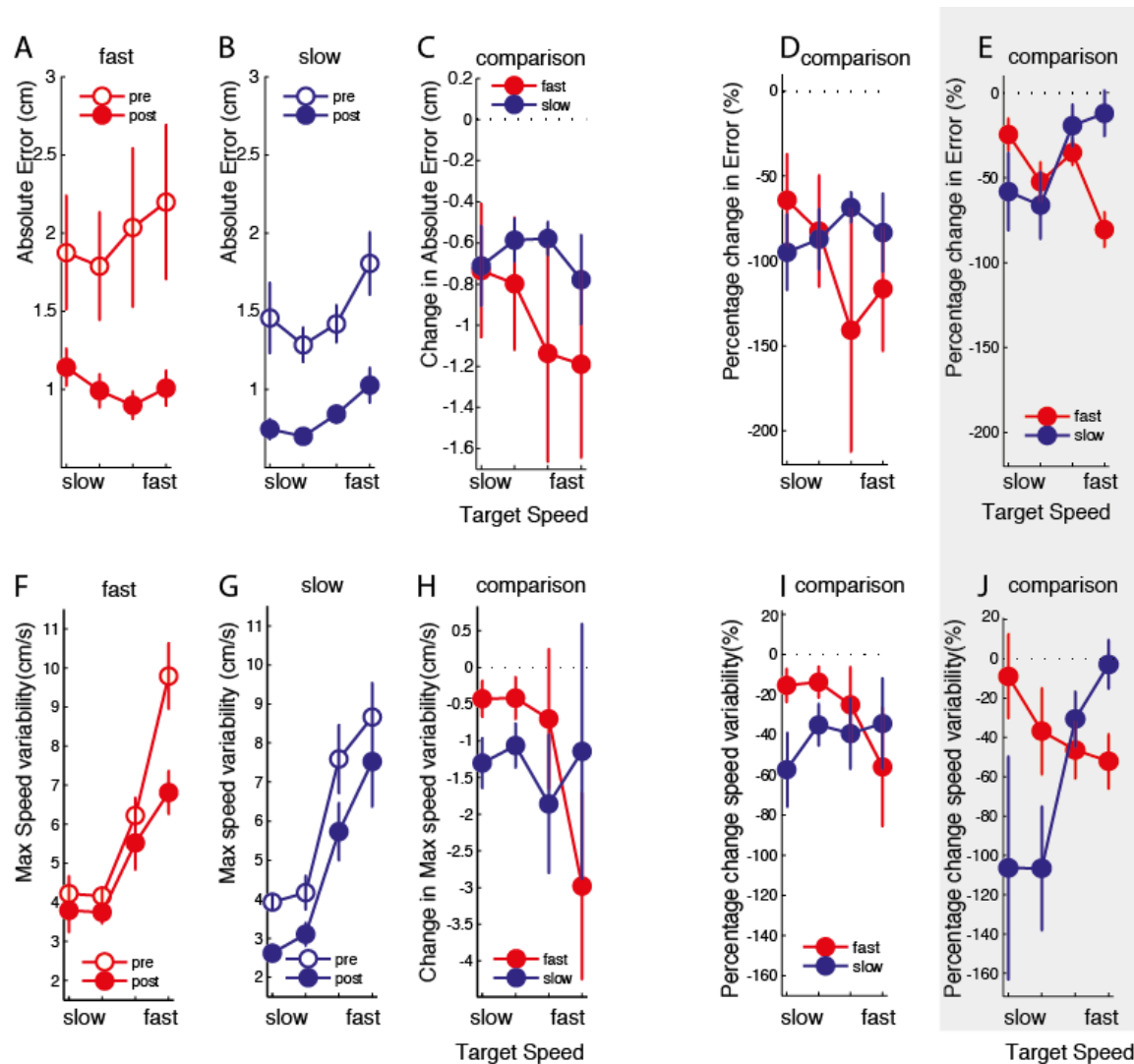


Figure 5.1. Comparison of learning observed in healthy individuals in new training protocol and protocol explained in chapter 4 (grey box). Reduction in absolute error (A-E) and maximum movement speed variability (F-J) after training. A) Average endpoint error for fast and B) slow training group (+/- SE) at each of the 4 individually set target speeds (slow to fast). Error is depicted in cm before (unfilled) and after (filled) training days. C) Comparison of change in endpoint error for the fast (red) and slow (blue) training group. Change of error depicted in percentage change for the current (D) and the previous (E) protocol.

Average maximum movement speed variability for fast (F) and slow (G) training group at each target speed before (unfilled) and after (filled) training. H) Comparison of change in movement speed variability for the fast (red) and slow (blue) training group. Change in movement speed variability expressed for the current (I) and previous (J) training protocol.

The percentage change in maximum movement speed variability (Fig 5.1 I&J), was not different in the fast training group ($F_{(3,42)} = 0.357$; $p=0.784$) using a 2wrmanova(MT(4)*GROUP(2)).

However, the changes in the slow training groups differed significantly between the protocols demonstrated by an interaction ($F_{(1.802, 25.228)} = 4.047$; $p = 0.034$). Post-hoc t-tests, a Bonferroni corrected t-test for multiple comparisons did not demonstrate significant differences between the groups at the various movement speeds.

We can therefore conclude that the new protocol, which incorporates stopping at the end of movement, promotes similar improvements in endpoint accuracy the primary outcome measure however reductions in movement speed variability are not the same. The greater reduction in maximum speed variability in the slow training group in the first experiment is probably due to the specific task requirements, where movement speed is completely unconstrained before training, allowing for greater improvements due to training (Fig 4.5 B & Fig 5.1. J). Because the same amount of learning was observed in the new protocol which is functionally more relevant to stroke patients I therefore used this new paradigm to investigate how training at two different movement speeds affects skill acquisition in stroke patients.

5.3.2. Participants

In these experiments I investigated the effect of fast and slow movement speed during training, on improvements of reaching accuracy in individuals affected by stroke.

Thirty-seven individuals affected by stroke (See table 5.1) (mean age: 57.5 years (SD 11.5); 10 females) without a history of a previous stroke or other concomitant neurological or musculoskeletal disorders were recruited to this six-day protocol. All patients had their stroke more than one year ago (mean: 4 years 9 months, (SD 3 years and 5 months)). The clinical presentations of all patients are presented in Table 1 and are divided for the two training groups (Fast and Slow). One patient's upper limb function deteriorated due to non-related medical complications between giving consent and attending for the initial assessment. As the patient consequently was not able to perform the training movement, he had to be excluded from the study. All other participants ($n = 36$) completed the 6-day protocol.

Table 5.1. Clinical presentation of research participants

ID	Age	Side	Onset	Fugl-Meyer		Spasticity		Sens	Mm	lesion	TMS	EMG
Fast Group				Pre	Post	Pre	Post					
SM02	30	R	132	40	41	3	3	NAD	3	haem	x	x
MC04	52	L	32	38	37	3	3	NAD	3	infarct	v	v
TB07	66	R	60	59	61	1	0	Aff	3	infarct	x	x
AC09	55	L	120	58	60	3	3	NAD	3	haem	x	x
JG10	49	L	15	32	32	3	2	Aff	1	infarct	v	v
BP11	54	L	12	51	49	3	3	Aff	3	infarct	v	v
MD14	88	R	84	51	57	1	1	Aff	3	infarct	v	v
CH15	60	L	36	48	54	3	3	NAD	3	infarct	v	v
BS17	69	L	84	61	60	0	0	Aff	4	haem	x	x
DT19	47	L	72	55	57	3	3	NAD	4	infarct	v	v
KP21	53	L	30	46	50	3	3	Aff	4	infarct	x	x
DB22	62	L	13	49	51	2	1	Aff	4	haem	x	x
HS24	68	L	22	24	26	1	1	NAD	3	infarct	x	x
IB25	58	R	42	49	52	1	1	NAD	3	infarct	v	v
YM27	49	R	28	49	49	3	3	NAD	4	infarct	v	x
AR30	74	L	15	63	64	0	0	Aff	3	infarct	v	v
AM33	49	L	52	39	43	3	2	NAD	1	infarct	v	v
NP34	47	R	72	62	62	0	0	Aff	4	infarct	x	x
MS36	50	L	19	38	42	2	2	NAD	2	haem	x	x
n=19	56.8	R=6	49.5	48.0	49.8	2	1.8	Aff=9	3.1	i=14	10	9

ID	Age	Side	Onset	Fugl Meyer		Spasticity		Sens	MM	lesion	TMS	EMG
Slow Group				Pre	Post	Pre	Post					
DC01	42	R	60	41	44	3	3	Aff	4	haem	x	x
MV03	69	L	24	58	62	0	0	Aff	4	infarct	v	v
MG05	47	L	28	57	58	3	3	NAD	2	infarct	x	x
ES06	56	R	48	41	37	3	3	NAD	2	infarct	v	v
KA08	37	L	30	62	62	2	2	Aff	3	haem	x	x
OA12	54	L	20	64	64	0	0	Aff	4	infarct	v	v
CM13	52	R	184	34	38	0	0	Aff	3	infarct	x	x
JP16	69	L	18	55	56	1	1	Aff	4	infarct	x	x
SD18	57	R	60	38	34	3	1	NAD	3	infarct	v	v
PB20	52	R	100	28	32	3	3	NAD	3	infarct	v	v
JE23	41	R	121	30	32	3	3	Aff	3	infarct	x	x
GB26	62	L	25	49	54	2	1	NAD	4	haem	x	x
CR28	45	L	30	55	57	1	3	Aff	4	haem	x	x
ES29	63	R	18	58	56	2	0	Aff	4	infarct	v	v
TB31	65	L	82	32	33	1	2	NAD	2	infarct	v	v
JP32	71	R	17	62	57	0	0	NAD	4	infarct	v	v
AS35	61	R	96	37	42	1	1	NAD	2	infarct	v	v
n=17	55.5	R=9	56.5	47.1	48.1	1.6	1.5	Aff=9	3.2	i=12	9	9

side= aff hand, Onset= time since stroke in months, sens=sensation (Aff=affected), mm=ant deltoid MRC grading, TMS & EMG: performed=v, not=x

5.3.3. Performance changes during training

The patients in the two training groups performed the training at different movement speed, improved their endpoint error, gained more points and reduced their movement speed variability over the 4 days.

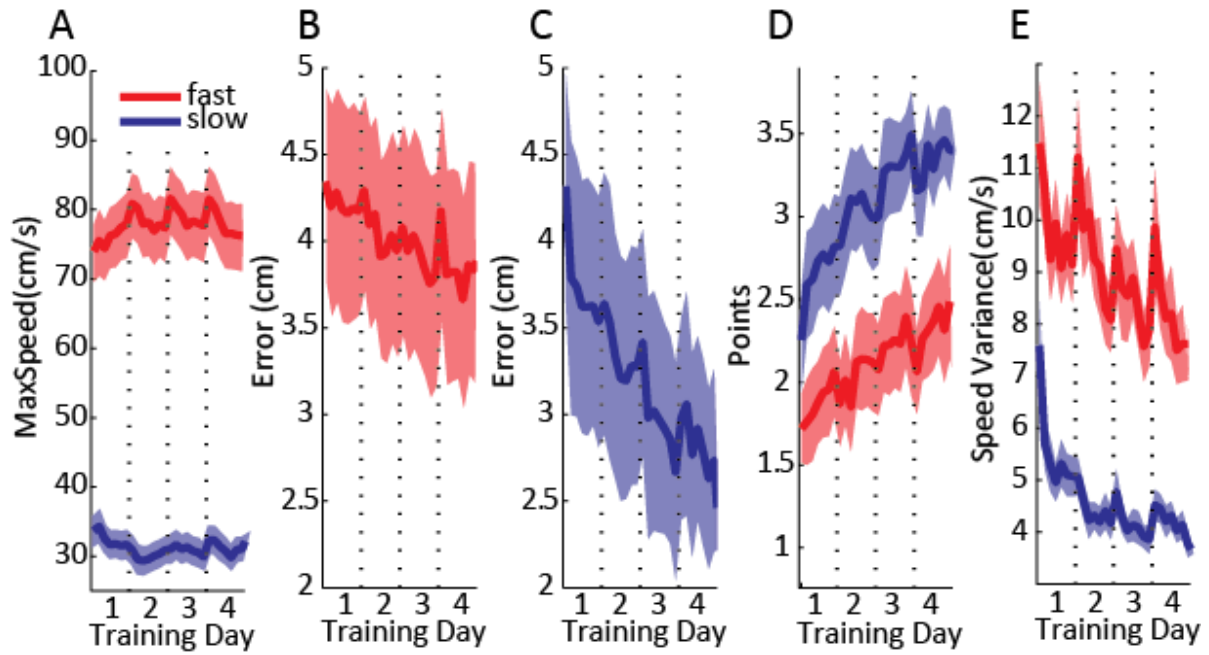


Figure 5.2 Reaching performance during training days (Day 1-4). A) Mean movement speed for fast (red) and slow (blue) group per training block (7/day) for the 4 training days. B) Mean endpoint error (RMS) for fast group for each training block during training days. C) Mean endpoint error for slow group for training days. D) Mean points per training block for the two training groups. E: Mean maximum speed variability (SD) for the two groups for each training block on the 4 training days.

In addition to the clear effects over the course of the 4 days, it also appears from the graphs (Fig 5.2 A-E) that there may be changes in performance during each day. Therefore I decided to do a 3 way ANOVA with BLOCK as another main factor. The movement speed (Fig 5.2A) between the groups was very different overall as stipulated by the two different protocols, thus a One way ANOVA demonstrated a difference in movement speed by and effect of GROUP ($F_{(1,34)}=91.847$, $p<0.001$). However, during each day of training the fast group gradually got slower over the training period whereas this was not the case in the slow training group. A 3w rmANOVA (BLOCK(7)*DAY(4)*GROUP(2) interaction ($F_{(18,612)}=31.350$, $p=0.003$) indicated that the change during the day (effect of Block ($F_{(6,204)}=4.281$, $p<0.001$)) differed between the groups. The movement speed of the slow group reduced on the first day from the first to the last block ($t_{(16)}=2.349$, $p=0.032$) and then remained stable over the 4 training days however; the fast group varied their movement speed.

On the first day the speed increased but not statistically and on consecutive days the initial velocity was the greatest and looked to be less in the last block of the training session (post-hoc t-test, Bonferroni corrected for multiple comparisons, show that this measure only reached significance on day 3 $t_{(18)}=3.369$, $p=0.018$). This could be indicative that patients training at the fast movement speed tired over the course of the training session.

There was no between-group difference in the size of the initial error (Fig 5.2B&C) ($t_{(34)}=-0.252$; $p=0.802$) despite very different movement speeds during training. The endpoint error reduced significantly over the 4 training days from the first training block to the last in the slow (Fig 5.2C) ($t_{(16)}=2.667$; $p=0.017$) but not the fast (Fig 5.2B) group however, no interaction was observed in a rmANOVA (Block(7)* Day(4)* Group(2)). The amount of error did differ between days (effect of DAY ($F_{(3,102)}=9.054$; $p=0.004$), as well as within each training day (effect of BLOCK($F_{(6,204)}=3.151$; $p=0.006$)).

These improvements were mirrored in the points that subjects received as a reward mechanism during training (Fig 5.2D). There was a difference in the amount of points awarded between the groups (Effect of Group ($F_{(1,34)}=6.724$; $p=0.014$)) but no interaction, demonstrating that the reward rate between the groups was similar. The amount of reward increased daily (effect of DAY ($F_{(3,102)}=20.834$; $p<0.001$) as well as per block throughout each day's training (effect of BLOCK ($F_{(6,204)}=6.9$; $p<0.001$)), indicating on-going improvement and learning throughout the training period.

Another measure of improved skill, a reduction in maximum movement speed variability during the training days, was investigated (Fig. 5.2E). There is a clear difference in the amount of variability between the groups (effect of Group($F_{(1,34)}=27.91$; $p<0.001$)), the slow group being less variable at the beginning (first BLOCK, day 1), ($t_{(34)}=2.640$; $p=0.012$) as well as at the end (last BLOCK, day 4) of the training period ($t_{(34)}=4.916$; $p<0.001$) in a Student unpaired t-test. The change in variability was however not statistically different between the groups. Both groups demonstrate a

continuous reduction in maximum speed variability on a day-by-day basis demonstrated by an effect of Day (4) ($F_{(3,102)}=9.72$; $p\leq 0.001$) as well as through-out every day by an effect of BLOCK (7) in a 3 way rmANOVA ($F_{(6,204)}=4.29$; $p\leq 0.001$). The graph (Fig 5.2E) suggests that retention of this reduced movement speed variability is poor. Forgetting can be confirmed by an effect of BLOCK ($F_{(1,34)}=10.675$; $p=0.002$) in a 3wrmANOVA (Block(2)*DAY(3)*GROUP(2). The ANOVA was performed comparing the first BLOCK of Day x with the Last Block of Day x-1. The forgetting observed differed on the days, effect of DAY ($F_{(2,68)}=5.988$; $p=0.004$), and a BLOCK*GROUP interaction approaching significance ($F_{(1,34)}=4.106$; $p=0.051$) was observed. This forgetting differed between the two training groups indicated by a main effect of GROUP ($F_{(1,34)}=38.278$; $p\leq 0.001$). However post-hoc t-tests, Bonferroni corrected for multiple comparisons did not confirm this difference between the groups.

5.3.4. *Performance changes after training*

5.3.4.1. *Absolute Error*

To investigate the effect of 4 days of training on the reaching ability at trained and non-trained movement speed I measured endpoint accuracy at the four set target speeds. Accuracy was defined as the Euclidean distance from the centre of the target before and after training. In figure 5.3 I show that the fast training group (Fig. 5.3 A) reduces their endpoint error for the trained (Target speed 4) but also for non-trained movement speeds (Target Speed (1-slow, 2-medium slow, 3-medium fast, 4-fast)). The same pattern is seen for the slow training group (Fig 5.3B) who reduced their endpoint error at their trained movement speed, namely target speed-1, but also for non-trained speeds. Since the baseline error was variable between individuals and an average improvement can misrepresent the amount of change in individuals with small error, I analysed improvement as a percentage change (See chapter 3). At baseline assessment there was no difference between the size of the error between the training groups as demonstrated by the absence of an interaction ($F_{(3,102)}=0.565$; $p=0.639$) or an effect of GROUP ($F_{(1,34)}=0.159$; $p=0.693$) in a 2wrmANOVA TargetSpeed(4)*GROUP(2). The percentage improvement in endpoint accuracy (Fig

5.3C) shows a training speed specific improvement in a 2wrmanOV by an interaction of Target Speed(4)*GROUP(2) ($F_{(3,102)}=3.217$; $p=0.026$) . Post-hoc analysis of change scores, Bonferroni corrected for multiple comparisons, did not find a significant difference at the various Target Speeds.

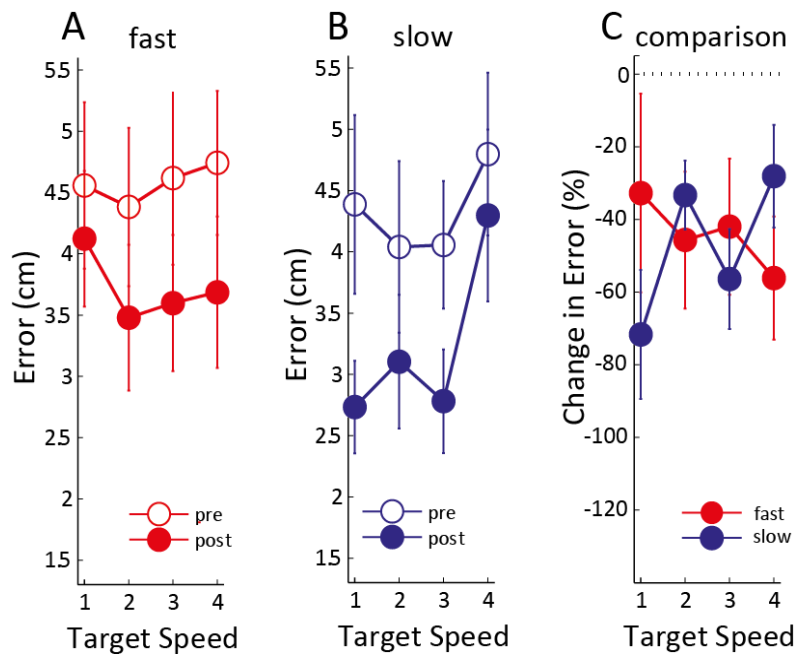


Figure 5.3. Changes in absolute error from pre to post-training testing. A) Average endpoint error for fast and B) slow (+/- SE) at each of the 4 individually set target speeds. Target speed 1=slow, 2= medium slow, 3=medium fast, 4=fast. Error is depicted in cm before (unfilled) and after (filled) training days. C) Comparison of change in endpoint error for the fast (red) and slow (blue) training group.

5.3.4.2. Variable Error

This reduction in error is not only evident in the absolute error but also in the distribution of the error around the mean (Reynolds and Day, 2005). A change in this error demonstrates reduced variability in the performance of a motor task (Georgopoulos et al., 1981) (See chapter 3.7.1 p.51). At baseline assessment there was a difference between the size of the variable error between the training groups as demonstrated by an interaction ($F_{(3,102)}=2.842$; $p=0.042$) but no effect of GROUP ($F_{(1,34)}=1.965$; $p=0.170$) in a 2wrmanOVA TargetSpeed(4)*GROUP(2) however post-hoc t-test, Bonferroni corrected for multiple comparisons, did not indicate a significant difference between the groups at any data point.

As this is the only measure where the baseline scores differed, the standard analysis techniques of analysing percentage change was maintained for this measure. The percentage reduction of the variable error (Fig 5.4) was different between the two training groups (Fig 5.4A-C) demonstrated by an interaction in a 2w rmANOVA TargetSpeed(4) GROUP(2) ($F_{(2.438, 82.885)}=6.093$, $p=0.002$). This was different between the GROUPS ($F_{(1,34)}=6.090$, $p=0.019$) however only at the slow TargetSpeed where the baseline error differed (Bonferroni corrected independent 2-tailed t-test $t_{(16)}=-3.432$; $p=0.012$).

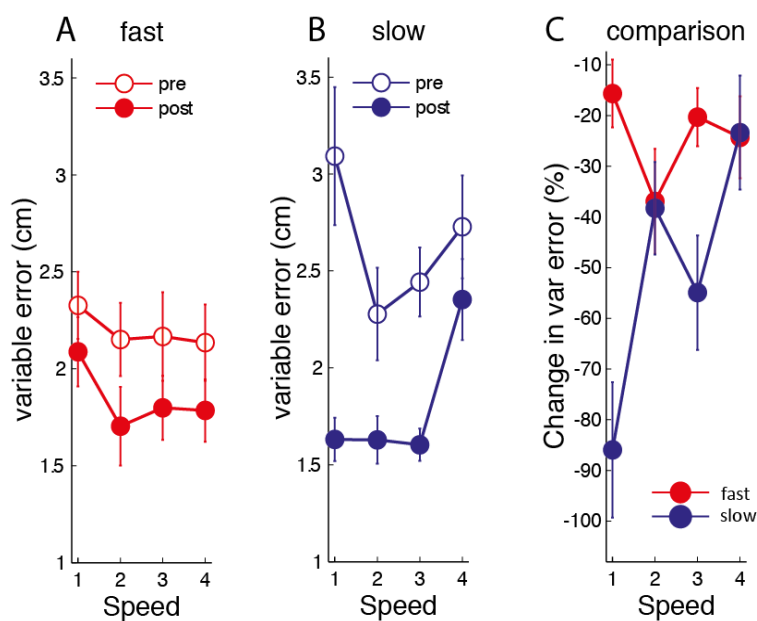


Figure 5.4. Variable endpoint error. A) Demonstrating the distribution of error around the mean absolute error for the fast(red) training group before (unfilled) and after (filled) training at the 4 set target speeds (1, slow; 2, medium slow; 3, medium fast; 4, fast) and B) for the slow (blue) training group. C) Compares the percentage of change in variable error observed at the 4 target speeds between the fast (red) and slow(blue) training group.

5.3.4.3. Signed error

In this population of stroke patients the distribution of the endpoint error around the target was not symmetrical. A bias to undershoot was observed (Fig 5.5A). This inability to reach the full 20cm could be due to a number of impairments. One impairment, spasticity could cause this undershoot due to an increased braking action of the stretched biceps during the reach. I therefore

investigated this by splitting participants into groups of individuals with mild and moderate spasticity. Individuals with moderate spasticity ($MAS \geq 1+$) tended to undershoot at all target speeds prior to training (mean=-2.62cm, SD=3.66cm) (Fig 5.5A) (One way ANOVA (SPASSEV); $F_{(1,43)}=14.403$, $p \leq 0.001$) in contrast individuals with mild spasticity ($MAS \leq 1$) ended their movement with only a small undershoot (mean=-0.55, SD= 2.50cm) (Fig 5.5B). The perpendicular error was also biased to end movement in the contra-lesional workspace for individuals with spasticity (mean=-1.43cm, SD=2.23) (Fig 5.5A) but not for individuals with no or mild spasticity (mean=-0.57, SD=1.59). This finding was confirmed by a. effect of spasticity severity in a one-way ANOVA ($F_{(1,143)}=6.522$, $p=0.012$).

5.3.4.4. *Parallel error*

Difficulties to perform outward reaching movements with increased clinical impairment after stroke are well established (Zackowski et al., 2004) however, the question is whether this translates into a greater error in extent of movement compared with direction. Therefore, to differentiate between changes in reaching extent and directional accuracy I divided the absolute error into a parallel (over-shoot and undershoot) and a perpendicular error.

There was no difference between the fast and slow parallel error before training. However the extent of the parallel error was altered by the training most notably at the trained speed (Fig 5.5E); the fast group improved their movement accuracy at fast speed and the slow group at the slow speed indicated by a TargetSpeed* GROUP interaction of the percentage change in movement accuracy (2w rmANOVA ($F_{(3,102)}=7.834$, $p \leq 0.001$). But Bonferroni post-hoc corrected t-tests could not confirm significant difference between the groups. The training speed specific improvement did not generalise broadly to non-trained target speeds, indicating two distinct mechanisms for improving performance at the different training speeds.

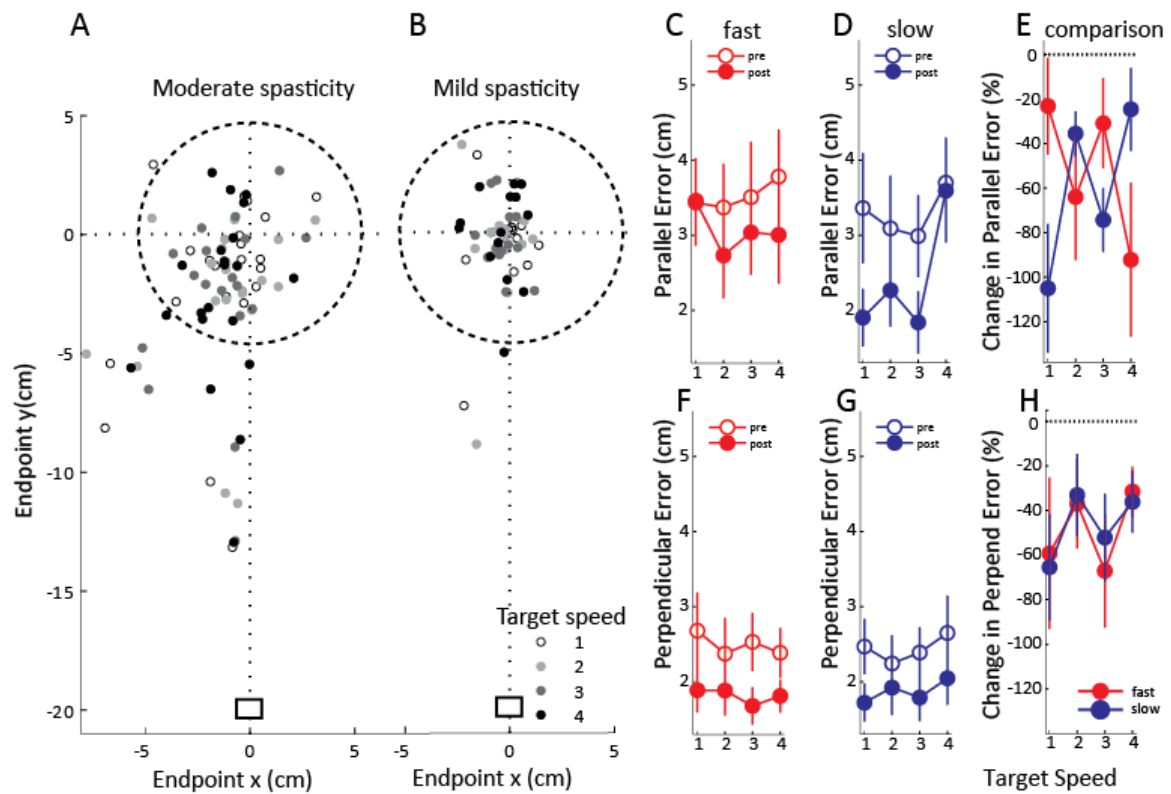


Figure 5.5. Distribution of endpoint error. A-B) Average endpoint location at the 4 set target speeds for each individual split for individuals with moderate (A) and mild (B) spasticity. Data of individuals with left hemiplegia is mirrored along y-axis. C-E). Parallel endpoint error for fast (C) and slow (E) training group. Presenting parallel error before (unfilled) and after (filled) 4 training days. E) Comparison of change in parallel error at the 4 target speeds for the fast (red) and slow (blue) training group. F-H) Perpendicular error for fast (F) and slow (G) training group and comparison between groups (H).

5.3.4.5. *Perpendicular error*

Perpendicular accuracy (Fig 5.5F&G) was very similar at high velocity and low velocity before or after training, without demonstrating a speed-accuracy trade-off. This error was significantly smaller than the parallel error at Fast($t_{(70)}=-2.398$, $p=0.019$), MedFast($t_{(70)}=-1.969$, $p=0.053$), and MedSlow target speed($t_{(70)}=-2.124$, $p=0.037$) but not at the Slow target speed($t_{(70)}=-1.495$, $p=0.139$). There was no difference of the perpendicular error before training between the two training groups. Interestingly very similar improvements were observed in this measure for both training groups (Fig

5.5F&G) and this generalised very broadly to all tested movement speeds (Fig 5.5H) demonstrated by an effect of TIME in a 3 way rmANOVA ($F_{(1,34)}=14.651$, $p=0.001$).

5.3.4.6. Movement speed variability

Because I wanted to probe possible factors that could contribute to the increased accuracy observed, I also measured how training altered the temporal variability of this movement. At baseline assessment there was no difference between the amount of movement speed variability between the training groups as demonstrated by the absence of an interaction ($F_{(3,102)}=1.112$; $p=0.348$) or an effect of GROUP ($F_{(1,34)}=0.610$; $p=0.440$) in a 2wrmanOVA TargetSpeed(4)*GROUP(2).

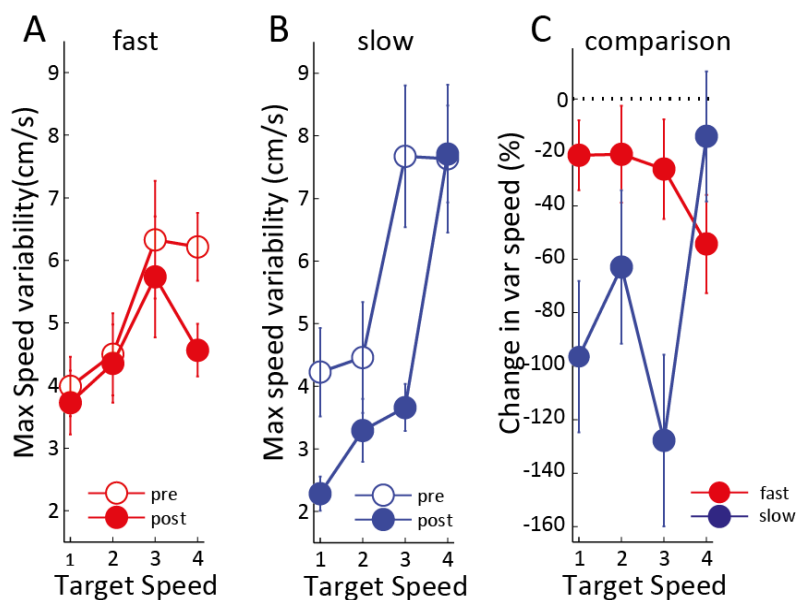


Figure 5.6. Comparison of changes in the variance of maximum movement speed A-C) due to training. A) data from the fast training group before (unfilled) and after (filled) training for set target speeds of 1-4. B) slow training group measures. Plot C) plots the percentage change of maximum movement speed variance for the two training groups.

The variability of the maximum movement speed (SD) (Fig 5.6) was reduced for both training conditions (Fig 5.6A&B) but specifically for the trained and closely related target speeds (Fig 5.6C) indicated by an interaction in a 2way rmANOVA ($F_{(2.455;83.483)}=4.428$; $p=0.010$). This improvement mirrors the changes observed in spatial performance but the training speed specific effect was not confirmed in Bonferroni adjusted post-hoc t-tests.

5.3.5. Influence of training on movement kinematics

The interactions observed in improved accuracy point to training-speed-specific improvements. This indicates that the two training groups learn something inherently different which can not be transferred for task achievement at the opposite target speed. I therefore analysed alterations in movement kinematics to investigate if the training altered the way that movements were performed. Changes in the shape of velocity profiles can indicate different learning mechanisms. Feedforward mechanisms tend to reduce the variability of the profiles whereas feedback learning mechanisms can skew the profiles by updating the command during movement (Shadmehr and Wise, 2005).

Because the reaching distance differed between individuals I expressed the distance as a percentage of a trial-by-trial mean amplitude (Fig 5.7). I have quantified this change in the velocity profile to measuring the point in the movement when peak velocity was reached. A perfect bell-shape would be half way through the movement as demonstrated in the fast training group before and after training. Overall the patients had a bell shaped velocity profile, but training changed the time of the peak velocity in a subtle way that differed between the groups and altered the area-under-the-curve (AUC) for the first half of the movement (Interaction, 2wrm ANOVA of TargetSpeed(4)* GROUP(2) ($F_{(3,102)}=3.451$, $p=0.019$). There was no difference of when maximum movement speed was reached in comparison to before training. In Bonferroni adjusted post-hoc t-test this difference was however not statistically significant.

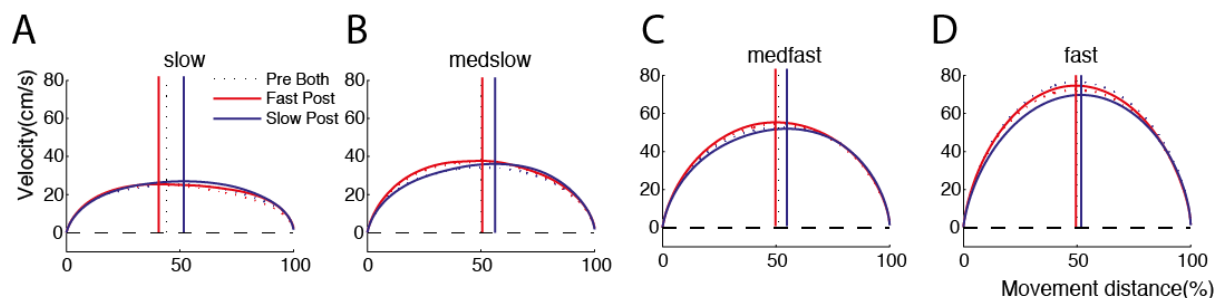


Figure 5.7. Changes to velocity profiles induced by training. Group average, interpolated to normalise reaching distance of fast(red) and slow (blue) group (A-D) at target speed 1 (slow)

(A), target speed 2 (medium slow) (B), target speed 3 (medium fast) (C) and target speed 4 (fast) (D).

In addition to the alterations in the velocity profile I can also quantify changes in the movement trajectory, here analysed as the straightness of the movement, namely the deviation from the direct path between the movement start- and endpoint. There was no difference between the length of the initial movement path between the training groups. All participants performed straighter reaching movements after training indicated by an effect of TIME in a 3wrmANOVA ($F_{(1,34)}=8.536$, $p=0.006$) (Fig 5.8) but there was no interaction or effect of group indicating that the improvement was no significantly different between the groups.

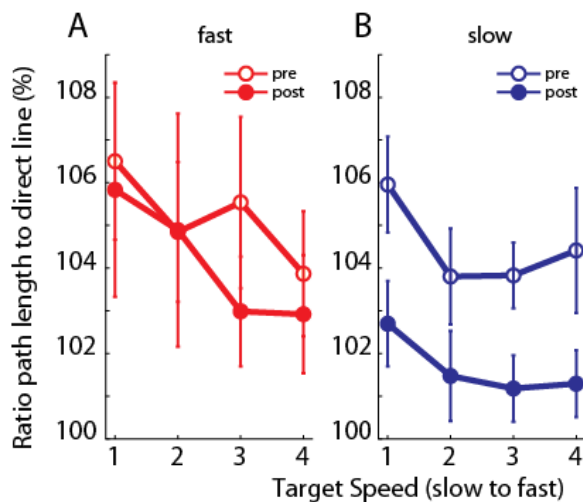


Figure 5.8. Movement path length before (unfilled) and after (filled) training calculated as a percentage of movement length divided by Euclidean distance between movement start and end position for fast (A) and slow (B) training group.

5.3.6. Training induced changes in impairment

5.3.6.1. Workspace

I further investigated if any improvement in reaching was confined to reaching with the arm in the manipulandum by investigating the functional workspace for the affected upper limb.

Individuals performed rotational supported and unsupported sweeping movements in both

clockwise and anticlockwise directions. (See example data of 1 participant Fig 5.9A for the different reaching conditions). Two datasets (1 from each training group) had to be excluded in this analysis because of poor quality of data. There was no significant difference between supported and unsupported reaches in either reaching distance nor area under the curve (AOC) and therefore the average measure are used during analysis.

The change in reach extent most closely reflects the trained movement and reductions in reach extent are a well-known limitation after stroke (Zackowski et al., 2004). Fig 5.9B shows the difference in the reaching distance in workspace (improved excursion in reach extent on the y-axis) before and after training for the two training groups. For supported reaches there was a effect of TIME($F_{(1,31)}=4.806$; $p=0.036$) in a 2wrmanOVA and post-hoc analysis indicated that the distance was not significantly increased for the fast however it was for the slow ($t_{(15)}=-2.228$, $p=0.032$) training group. For unsupported reaches the effect of TIME ($F_{(1,31)}=3.951$; $p=0.056$) was only approaching significance. The average increase in reaching distance in the slow training group was 6.2 cm (SD+/- 6.8cm) and 5.3 cm (SD+/- 8.2cm) for the supported and un-supported reaches respectively.

No interaction or effect of Time was observed when investigating changes in the AOC.

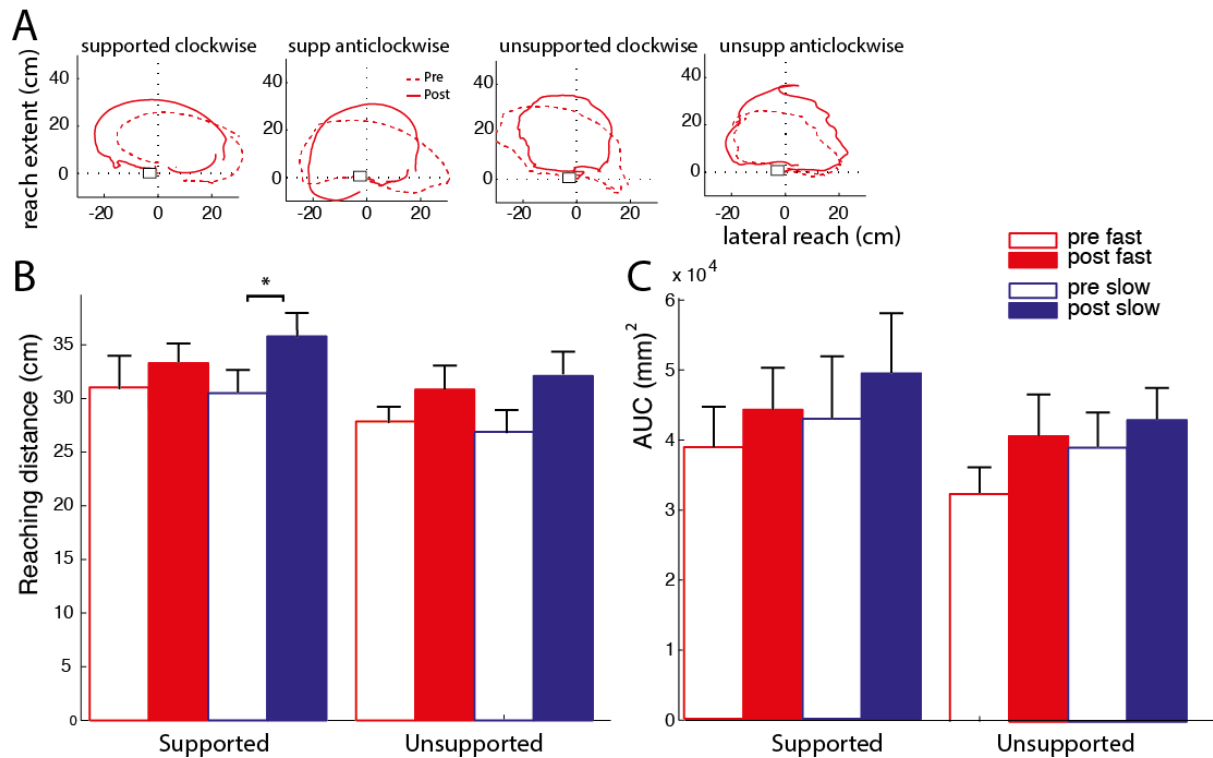


Figure 5.9. Workspace. A) Reaching path of a representative participant for performance on workspace task before (dashed) and after (solid line) training in supported clockwise, supported anti-clockwise, unsupported clockwise and unsupported anti-clockwise direction. Mean reach extent (B) and AUC (C) before (unfilled) and after (filled) training for fast (red) and slow (blue) training group during supported and unsupported reaches.

5.3.6.2. Spasticity

Another impairment, biceps spasticity measured with the modified Ashworth scale (Fig 5.10A), reduced in the group training at fast movement speed. (Related samples, Wilcoxon signed rank test, $p=0.046$) but not for the individuals training at slow movements $p=0.581$. Similarly the changes in measures of the Fugl-Meyer upper limb subset (Fig 5.10B) were significant for the fast training group, $p=0.004$ but not for the slow training group ($p=0.230$). Both of these changes are very small improvements and are not clinically significant, however it is interesting that such a brief training period of 4 days was able to induce a reduction in impairment in this group of chronic stroke patients and that fast training did not increase spasticity but actually reduced it.

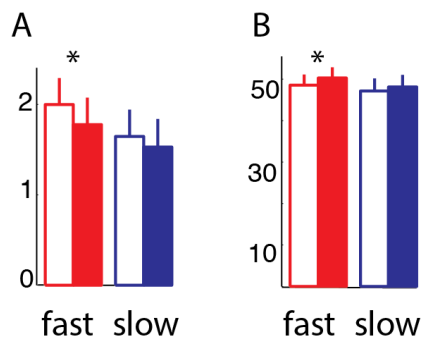


Figure 5.10. A) Mean spasticity and B) Fugl-Meyer score for the fast (red) and slow (blue) training groups before (unfilled) and after (filled) training.

5.3.7. Influence of impairment on performance and learning

The relationship between a number of measures of impairment, the ability to perform the reaching movement at baseline and the amount of improvement observed was investigated. Because impairment measures using the MAS for spasticity and the MRC grading system for muscle weakness are very coarse and sensory function is binary, I performed an a priori classification median split of spasticity, muscle weakness and sensory impairments, resulting in binary measures. This also prevented subdivisions of the population into smaller uneven groups making interpretation difficult. This median split resulted in groups of only relatively similar sizes as the coarse measure density of these impairments did not allow for greater distinction. Spasticity was split for individuals with no or minimal spasticity ($n=15$) (MAS=0 and 1) and individuals with moderate spasticity ($n=21$) (MAS=1+ and 2). Muscle weakness was divided for individuals with minimal or no muscle weakness ($n=14$) (≥ 4 on Medical Research Council (MRC) muscle power grading) and moderate weakness ($n=22$) (≤ 3 MRC) and sensory impairment for individuals with no or minimal difficulties with discriminating light touch ($n=18$) (accuracy $>80\%$ on sensory testing) and individuals with significantly impaired sensation ($n=18$) ($<80\%$).

5.3.7.1. Influence of impairments on baseline performance

Sensory impairment after neurological incident is known to influence the ability to relearn movement (Vidoni and Boyd, 2009), however interestingly when investigating the effect that

sensory impairment has on baseline performance (Fig 5.11A) of the reaching task, individuals with moderate sensory deficits (<80% accuracy on the two-point discrimination and light touch testing), did not perform worse at the task; in contrast they appeared to be better but this was not significant (Independent sample t-test, $t_{(34)}=1.633, p=0.112$). Spasticity also appeared to influence baseline performance.(Fig 5.11B) . Patients with no or minimal spasticity had smaller endpoint error than individuals with moderate spasticity (Modified Ashworth Scale=1+ and 2) however this was only approaching significance (Independent sample t-test, $t_{(34)}=-1.872, p=0.070$). Another impairment measure, muscle weakness (Fig 5.11C), strongly influenced the performance prior to training . Greater muscles weakness (Deltoid muscle power ≤ 3) reduced reaching accuracy in comparison to mild muscle weakness (MRC ≥ 4) (Fig 5.11C) $t_{(34)}=-2.399, p=0.022$.

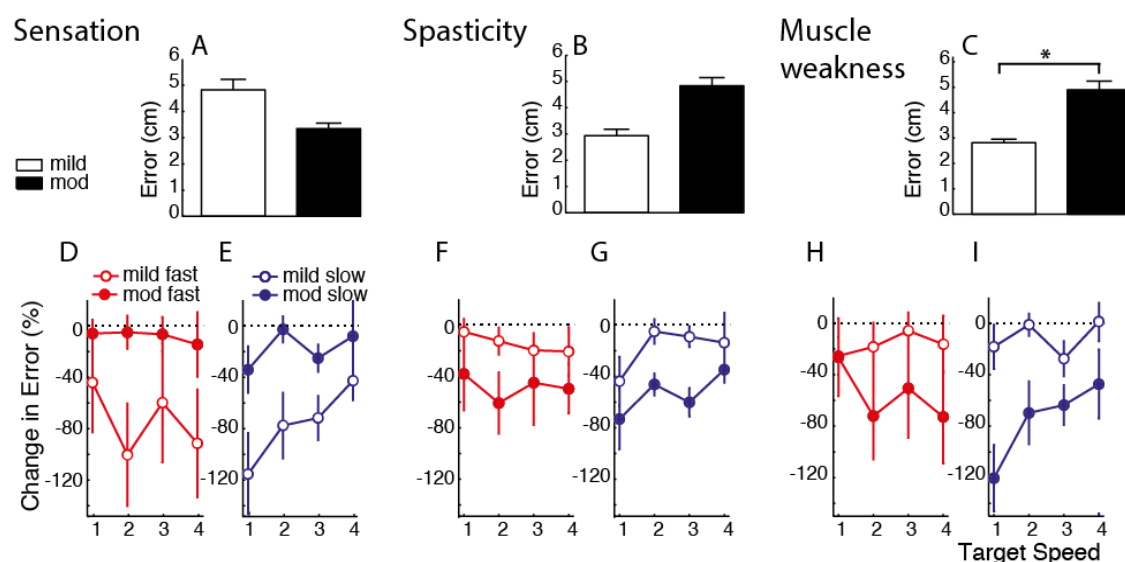


Figure 5.11. A-C) Influence of level of impairment on baseline performance in reaching task for mild (unfilled) and moderate (filled) A) sensory impairment, B) spasticity (Modified Ashworth score) and C) Muscle weakness score. D-I) Influence of impairment level (mild (unfilled) and moderate (filled)) on learning in the fast (red) and slow (blue) training group. D-E) sensory impairment, F-G) spasticity and H-I) muscle weakness.

5.3.7.2. Influence of impairment on learning

I further investigated how these impairments influenced learning in the two training conditions (Fig 5.11D-I). Individuals presenting with significant sensory impairment demonstrated

very limited improvement of the endpoint error in comparison to individuals with intact sensation. This finding was evident for both the fast (Fig 5.11D) and the slow (Fig 5.11E) training condition. When combining the training groups to investigate the effect of sensory impairment on the percentage change an effect of SEVERITY can be observed in a rmANOVA $SEV(2)*TARGETSPEED(4)$ ($F_{(1, 34)}=4.921$; $p=0.033$) however no interaction was observed between SEVERITY and TargetSpeed.

I expected that spasticity would also influence the ability to improve at this task but interestingly individuals with moderate spasticity appeared to improve more in both the fast (Fig 5.11F) and in the slow (Fig 5.11G) training group however this was not statistically significant. Individuals with greater spasticity had a greater error prior to training and therefore a greater reserve to improve.

Muscle weakness has been established to be a major contributor to functional limitations (Zackowski et al., 2004). In this set-up in the slow group the severity of muscle weakness had a significant influence on the ability to learn (Fig 5.11H-I) demonstrated by a $SEV(2)*TargetSpeed(4)$ interaction ($F_{(3, 45)}=3.967$; $p=0.014$). Individuals with more weakness were able to learn more and similarly to the improvements for the individuals with spasticity these individuals also had worse performance at baseline.

5.4. Discussion

In this study I instructed chronic stroke survivors to perform centre out reaching movements to a target at four individually defined movement speeds. For 4 consecutive days individuals performed intensive training to improve their reaching accuracy at either high or low velocity. I analysed the effect of this training on movement accuracy, movement kinematics and how the individual's clinical presentation affected learning.

Individuals could only improve in the task by better task performance and could not use compensatory strategies. Despite this, individuals improved their endpoint accuracy. There was no difference between the two training groups, training either at fast or slow movement speed, in the amount of improvement at the trained speed. The effect of training did not generalise to speeds far removed from the training speed. Training in this very simple task also produced small improvements in clinical scales and in measurements of workspace area, indicating that the training generalised to other tasks. Interestingly there was no sign that training at fast movement speed increased spasticity.

We established individual's maximum movement speed while performing this task and used this to determine the testing and training speed on an individual basis. Although it would have been interesting to know what each individual's preferred movement speed would have been before training, in this protocol we did not obtain this information. A reliable measure of preferred speed could have confirmed whether stroke patients move slower with the affected and/or the unaffected upper limb. We expected that for stroke patients a laboratory based reaching task in a robotic manipulandum would be very foreign and thereby strongly influenced by instruction.

5.4.1. *Improved endpoint accuracy after training*

In this study protocol patients had to perform a large number of repetitions of this reaching task. The high number of repetitions of the training was tolerated but a decline in performance could be observed at the end of each training day, particularly in the fast training group. This might

indicate that the intensity was near, or at the limit of the patients' performance. However, the patients did not forget what they had learned on the previous day which may indicate that training was sufficient to reinforce consolidation of the new skill (Reis et al., 2009).

Individuals in both training groups improved their performance and this was evident at an impairment level in increased movement accuracy and a reduction in performance variability. The greatest improvements were evident in the parallel error at the trained movement speed. This improvement consisted of a reduction of the spread of the movement endpoint and approached significance for the reduction of the bias to undershoot. The increased performance was also reflected in reductions in the variability of the maximum movement velocity suggesting use-dependent learning mechanisms as observed in animal models and healthy individuals (Georgopoulos et al., 1981, Verstynen and Sabes, 2011, Hammerbeck et al., 2014). Yet generalisation to movement speeds closely related to the trained speed were observed in both groups, which was not the case for very different movement speeds.

5.4.2. Generalization to other context and other speeds

Generalisation of an acquired skill is vital in rehabilitation after neurological injury as it would be impossible to train all movements required for reacquisition of independence. A common concern about training in robotic devices is that transfer of learning to functional activities is limited (Mehrholz et al., 2012), and the inability to generalise learned behaviour has been found to be more pronounced in the chronic stage (Masiero et al., 2011). Training in robotic devices promotes recovery on an impairment basis and transfer has been shown to be dependent on training structure (Kluzik et al., 2008). Stroke patients performing the slow movement training showed transfer of reduced undershoot to greater reach extent in workspace analysis on a table removed from the robotic device. The improvement was observed in supported reaching movement but also in unsupported reaches, which represents a far more functional movement. Reduced reach extent is a common impairment after stroke with significant influence on upper limb function (Zackowski et al.,

2004, Ellis et al., 2011). Our set-up could only measure movements performed while the arm was supported on the table and these points were anterior of the starting position. Therefore analysis measured the increased excursion in the Cartesian 'y' direction, from the start of the movement as well as increases of area under the whole reaching curve anterior of the starting position although changes in the movement could have occurred in all directions.

Experimentally, generalisation patterns to non-trained movement speeds in healthy individuals have been shown to be variable (Shadmehr and Wise, 2005, Francis, 2008, Joiner et al., 2011, Shmuelof et al., 2012). In our study in stroke patients, improvements in parallel accuracy and movement speed variability, in both training groups did not generalise broadly to other movement speeds. The finding that generalisation decayed with variance from the trained velocity mirrors generalisation patterns observed in reaching movements in healthy subjects (Francis, 2008, Hammerbeck et al., 2014).

I expected less generalisation from slow training to fast movement speed because at greater velocity, altered interaction torques arise which require changes in the combination and magnitude of joint movements (Morasso, 1981, Russo et al., 2014). A greater rate of acceleration increases the net joint torques, by increased muscle activation and visco-elastic load, as well as the inertial load on the system (McCrea et al., 2002). It is known that the ability to predict these altered limb dynamics with varying velocities, and to adjust to them by changing the feed-forward command, are reduced in stroke subjects (Levin, 1996, Beer et al., 2000). The limited transfer to slow movement of the fast training group might indicate a more global difficulty to adjust movements to altered torques and reinforces our assumption that it is important to experience a variety of velocities during training.

I propose that the training-speed-specific learning in both groups demonstrates use-dependent motor learning in this population of chronic stroke survivors. The inability to perform the task at a different speed, indicates that the two training groups did however learn something different which is not transferable with altered demands at changed movement speed.

5.4.3. Potential learning mechanisms at different speeds.

In this study both training groups reduce their endpoint error and movement speed variability demonstrating improved control of movement. The positively skewed velocity profiles and straighter trajectories after training for the slow training group are consistent with studies indicating greater reliance of integration of feedback information, a form of somatosensory learning (Ostry et al., 2010). During slow movements, individuals have the opportunity to improve their performance by using proprioceptive feedback during the movement (Shadmehr and Wise, 2005) as previously observed in healthy individuals training at slow movement speed (Francis, 2008, Hammerbeck et al., 2014). Training promotes the formation of a use-dependent tendency to skew velocity profiles and reach maximum movement speed later in the movement not only at trained but also at untrained movement speeds (Hammerbeck et al., 2014). Additionally stroke patients performed straighter movements, whereby they possibly reduce the size of their motor output and thereby the signal dependent noise (Harris and Wolpert, 1998) reinforcing reduced variability in movement speed and endpoint spread at the trained movement speed.

In contrast the fast training group did not show these signs of feedback learning mechanisms. Movement velocity during training was very fast which makes integration of feedback during task performance difficult. The improvements in the fast group are probably due to feed-forward learning processes involved with force control and motor planning (Seidler et al., 2004). This requires an internal model of accuracy acquired through practice and knowledge of previous results. The outcome of previous reaches is used to update and alter the motor command for consecutive reaches (Georgopoulos et al., 1981, Shadmehr and Wise, 2005). Reductions in endpoint variability and movement speed variability, most probably as a result of a better motor command, could be observed for the fast training group but conclusive evidence that feedforward learning is the underlying mechanism whereby the fast group improves the movement accuracy, i.e. reduced motor variability in the initial part of the movement, was not evident. This could be due to the fact that the training protocol is only 4 days and therefore individuals might still be performing the task

with a lot of task variability, as demonstrated in the data of the training days, with insufficient training time to optimise the feed-forward command.

5.4.4. The effect of fast movement on spasticity

Increased muscle tone was assessed using the modified Ashworth scale (MAS). This scale is standardly used in clinical practice as well as in research paradigms however it does not have the ability to differentiate between neural (i.e spasticity) and non-neural (i.e. mechanical changes to muscle fibres, increased connective tissue and changes in tendon properties) contributors to the increased resistance to movement, observed after neurological disease (Dietz and Sinkjaer, 2007).

Individuals affected by stroke and other neurological conditions move more slowly, although they are able to move at higher velocity without further deterioration of movement quality (Mazzoni et al., 2007, van Vliet and Sheridan, 2007, DeJong et al., 2011). Fast movements are not specifically encouraged in rehabilitation paradigms and this hesitance probably stems at least partly from the fear of increasing spasticity, a velocity dependent muscle stiffness observed after stroke (Bobath, 1990, Pandyan et al., 2005). This fear and avoidance of fast movement speed does however appear to be ungrounded as similarly to strength training (Ada et al., 2006) training at high movement velocities did not increase spasticity. Moderate hypertonus, measured by the modified Ashworth scale did not interfere with the ability to improve motor performance and decreased after training for the fast training group, in keeping with findings that continual repeated movements can have temporary beneficial effects on spasticity (Schmit et al., 2000).

In this training protocol individuals with higher modified Ashworth scores, indicating greater muscle stiffness (Dietz and Sinkjaer, 2007), had greater difficulties with performing accurate reaching tasks. Increased muscle stiffness is known to affect movement performance (Sorinola et al., 2009), possibly due to an inability to produce sufficient joint torques due to over-active antagonist activity (Lum et al, 2004, Levin et al, 1996) and altered properties of contractile soft tissue (Dietz and Sinkjaer, 2007). However, I found that movement trajectories at high velocities were straighter

during fast movements indicating that velocity dependent tone did not disrupt the quality of reaching movements.

The increased neural firing observed due to spasticity during rest, the standard state for assessing the severity of hypertonus with the MAS, is not evident during movement (Mottram et al., 2009). During movement, spasticity results in impaired modulation of firing to various output requirements (Ibrahim et al., 1993, Mottram et al., 2009, Mottram et al., 2014). The reduction of hypertonus observed in the fast training group might be achieved by exposure to a variety of movement speeds increasing motor unit recruited (Mottram et al., 2014) and the ability to modulate firing patterns. Another possibility is that the reduction in hypertonus observed in the fast training group is due to alterations, and greater compliance of non-neural contractile components (Dietz and Sinkjaer, 2007), due to high repetition of explosive muscle activations and resultant biceps stretches during the training days. However, the current trial design does not allow us to differentiate between these interesting mechanistic causes of a reduced MAS score.

None the less the individuals with greater muscle stiffness in this training protocol were able to perform repetitive training, consisting of over 400 reaching movement, and improve their endpoint accuracy at high velocity.

5.4.5. The influence of clinical presentation on performance and learning

Stroke results in a number of impairments affecting upper limb movement and function. The findings of this study are in line with previous studies highlighting the importance of muscle weakness for motor performance and movement speed (Zackowski et al., 2004, Wagner et al., 2006, Sorinola et al., 2009, Chang et al., 2013).

I further investigated how different impairments affect learning at various movement speeds. Neither muscle weakness nor spasticity influenced learning at either training speed however, sensory impairment reduced learning for both groups. This finding supports studies reporting that sensory feedback is required during the movement to alter the movement path

(Vidoni and Boyd, 2009) as well as for consecutive movements to update the motor command (Todorov and Jordan, 2002, Vidoni and Boyd, 2009). We here tested participant's sensation by two-point discrimination on the tip of the index finger as well as light touch in the palmar and dorsal aspect of the hand with the use of monofilaments. These measures pose two problems; firstly we tested distal rather than proximal sensory ability, however muscle strength was measured proximally and training required proximal upper limb movements. The extent of proximal impairment is therefore not known nor whether proximal sensory impairment would indeed affect baseline performance and learning to the same extent. Sensory impairment was however classed very broadly as intact or impaired and individuals with absent sensation were excluded. Busse and Tyson, demonstrated substantial agreement between palm and hand dorsum testing and whole limb sensation with such broad classification (Busse and Tyson, 2009). The other significant shortfall in this design is the lack of a measure of proprioception, a vital sensory modality specifically for this kind of task where visual feed-back is withheld. Previous work has been performed to measure the contribution of proprioception to motor learning (Ostry et al., 2010) and found that learning comprises a combination of somatosensory as well motor learning. Without an outcome measure of proprioception before and after training the contribution of somato-sensory learning can not be assessed or quantified in this paradigm.

5.5. Conclusion

In this study individuals affected by stroke improved their endpoint accuracy when reaching at both fast and slow movement speed. Training at fast movement speed was not detrimental to spasticity but actually reduced it.

The limited transfer of movement skill to non-trained movement speed has potential clinical implications. To achieve greater learning and improved performance in related tasks, training needs to be varied exposing individuals to a spectrum of similar but distinct movement patterns (Braun et al., 2009) and possibly also movement speeds. Whether performing this training while including a

variety of movement speeds would result in greater transfer or better task performance would however need to be investigated. That being said incorporating movement at higher velocities in rehabilitation paradigms will prevent the reinforcement of slow movements and potentially increase the ability to predict and counteract altered joint torques during movements at higher velocity.

6. Cortical connectivity and learning after stroke

6.1. Introduction

In chapter 5, I investigate how chronic stroke patients improve their endpoint accuracy and clinical impairments due to training at either high or slow velocity. I further wanted to explore if stroke patients with greater prevalence of ipsilateral projections from the unaffected hemisphere to the weak limb benefitted the most of proximal arm training and if this increased the effectiveness of these connections (Bradnam et al., 2013) in comparison to connections from the affected hemisphere.

Whether training induced improvements of proximal arm function relies exclusively on increased efficiency of contralateral corticospinal pathway from the damaged hemisphere (Schwerin et al., 2008, Barker et al., 2012) or if re-wiring by other pathways (Lemon, 2008) and specifically the ipsilateral connections from the unaffected hemisphere (Bradnam et al., 2013) play an additional role is not clear in human stroke survivors. Proximal muscles have greater ipsilateral connectivity which is inversely correlated to the amount of direct cortico-motoneuronal connections, probably an indicator of greater involvement in bimanual and axial activity (Palmer and Ashby, 1992, Marsden et al., 1999, Ziemann et al., 1999, Bawa et al., 2004). The prevalence of recruiting these pathways with transcranial magnetic stimulation is increased after stroke (Turton et al., 1996, Traversa et al., 1998, Ziemann et al., 1999, Alagona et al., 2001, Buetefisch et al., 2005, Swayne et al., 2008, Bradnam et al., 2011, Barker et al., 2012) but the functional relevance of these pathways to recovery has not been clearly established.

Studies investing the effect of arm training on it's own and in combination with brain stimulation have demonstrated mixed findings in increasing the reliance of the corticospinal connections from the affected hemisphere (Bradnam et al., 2011, Barker et al., 2012) but, in animal studies recovery of arm function was found to be correlated to increased connections from the unaffected hemisphere (Zaaimi et al., 2012) . The theory that the unaffected hemisphere improves functional outcome by direct ipsilateral connections to the motoneurons of the affected limb has

now been largely dismissed (Palmer et al., 1992, Turton and Lemon, 1999, Alagona et al., 2001) however, recently the interest in the role of this hemisphere has re-emerged questioning it's role in driving brainstem pathways to the affected limb (Schwerin et al., 2008, Swayne et al., 2008, Bradnam et al., 2011, Fisher et al., 2012, Zaaimi et al., 2012).

I here investigated corticospinal connectivity of a sample of chronic stroke patients conducting the high repetition reaching training protocol, described in chapter 5, with either an emphasis on fast or slow movement speed during training. I wanted to establish 1) the occurrence and pattern of proximal upper limb responses when stimulating the affected and the unaffected hemisphere. I further 2) wanted to investigate how these responses are related to functional impairment. 3) Lastly I wanted to analyse the effect of training on the prevalence and magnitude of responses in the two pathways to establish if ipsilateral projections from the unaffected hemisphere are important in proximal arm recovery after stroke.

The hypothesis for this experiment was that reaching training in chronic stroke patients would change the excitability of cortical pathways to the affected upper limb. We wanted to investigate if this change was driven by increased connectivity from the affected or the unaffected hemisphere, and if the movement speed during training affected the strength and the pathway of this effect.

6.2. *Methods*

6.2.1. *Participants*

Of the 37 patients recruited for our reaching study 19 patients were eligible and gave consent for single pulse transcranial magnetic stimulation before and after training. These participants consisted of 10 individuals performing training at high movement velocity and 9 individuals training at low velocity (Table 5.1).

6.2.2. *TMS protocol*

EMG was recorded with self-adhesive AG/AgCl electrodes (Skintact®) placed over the muscle belly of bilateral biceps brachii, triceps brachii (lateral head), anterior deltoid and horizontal fibres of pectoralis major. The electrodes were positioned in-line with the muscle fibres ~2cm apart after skin impedance was reduced by cleaning the skin and using an abrasive scrub (Nuprep Skin Prep Gel, Weaver and Company, USA) in accordance to SENIAM EMG recording recommendations (Hermens et al., 2000). Methods proposed by Kendall McCreary et al, (Kendall McCreary et al., 2010) were followed to ensure correct electrode placement and verified by inspecting the EMG activity. The cathode was always placed proximally and the anode distally over the muscle belly (Loeb, 1986). The reference electrode was placed over the bony prominence of either the acromio-clavicular joint or the clavicle (Hermens et al., 2000).

EMG signals were amplified and filtered (20 Hz to 1kHz) with a D360 amplifier (Digitimer Limited Welwyn Garden City, UK). The signals were sampled at 5 kHz and digitised using a laboratory interface (Power 1401, Cambridge Electronics Design(CED), Cambridge, UK) and stored on a personal computer for display and off-line data analysis.

Single pulse TMS was delivered using a 70-mm figure-of-eight shaped TMS coil and a Magstim 200 magnetic stimulator (Magstim Company, Whitland, Dyfed, UK). The stimulator produced a monophasic pulse with a rise-time of approximately 100µs decaying back to zero over approximately 0.8ms. The coil was placed tangentially over the scalp with the handle pointing

postero-laterally at 45 degrees to the sagittal plane inducing a posterior-anterior current in the brain (Fig. 6.1).

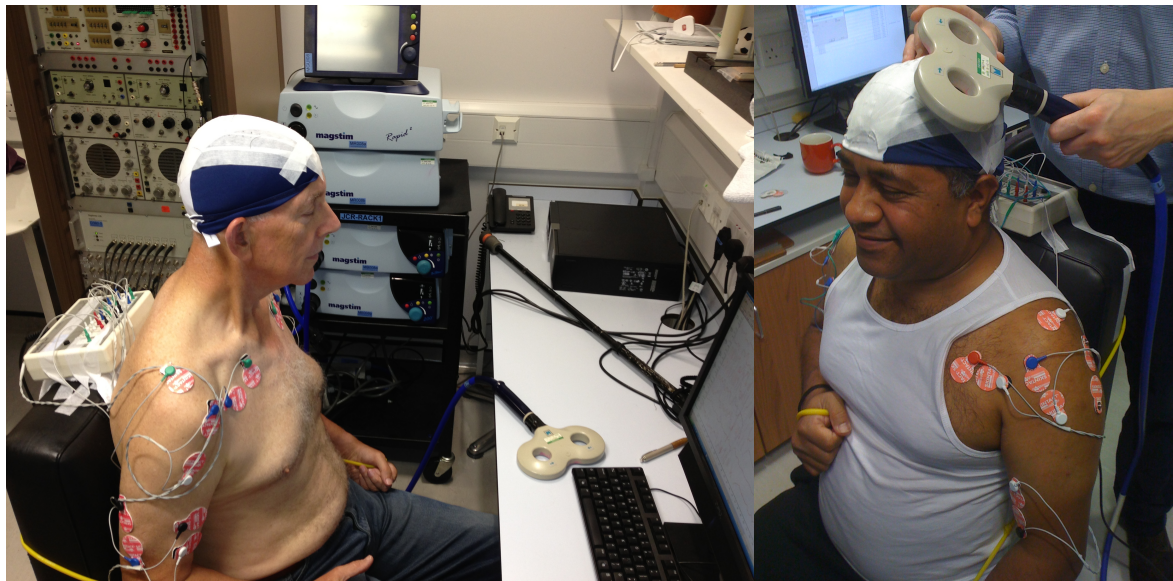


Figure 6.1. Positioning and EMG placement for transcranial magnetic stimulation.

I monitored MEP responses with electromyography (EMG) for bilateral biceps brachii, lateral head of triceps brachii (lateral head), anterior deltoid and horizontal fibres of pectoralis major muscles by inspecting traces sampled from 1000ms before to 2200ms after stimulation (Fig.6.1). Before every stimulation, muscles were activated, by performing a bilateral reaching movement against a weak elastic band. Individuals were instructed to reach forward with both arms at a comfortable pace. Muscle activity was displayed on the computer desktop and the experimenter monitored these and only delivered stimulation when clear evidence of activity was observed. Individuals were encouraged to increase the muscle activity of the affected upper limb if poor activation was observed in EMG traces.

The 'motor hotspot' for MEPs of the hemiplegic shoulder muscles was determined initially for the unaffected hemisphere. The motor area of proximal upper limb muscles was mapped by giving three stimulations at 70% MSO per site over a 3x3 1cm grid centred 3cm lateral and 1 cm anterior of the vertex, over the proximal upper limb representation in the primary motor cortex

(Wassermann et al., 1992). The grid was marked on a cap on both hemispheres. After mapping, MEP's were averaged offline per stimulation site and visually inspected for the greatest amplitude and consistent activation of the affected pectoralis major, anterior deltoid and triceps lateral head. The hotspot was determined as the location with the best responses, if any, of the affected ipsilateral upper limb muscles. If no responses were detected in the affected upper limb the site with the optimal contralateral responses was used.

A train of 20 stimulations was delivered to the hotspot at 70% MSO while performing the same reaching movements to achieve pre-activation while bilateral MEP's were recorded. Thereby contralateral and ipsilateral MEPs were measured stimulating the unaffected hemisphere (Unaffected contralateral(UC) and unaffected ipsilateral (UI) respectively) (Example trace stimulating unaffected left hemisphere and acquiring UC responses in right and UI responses in left upper limb Fig 6.2).

The procedure was repeated for the affected hemisphere but the optimal stimulation site for the muscles of the affected contralateral upper limb, if any, was now established. If no hotspot was evident the centre of the grid was used as the hotspot. Responses of the contralateral and ipsilateral MEP's were established when stimulating the affected hemisphere (AC and AI respectively).

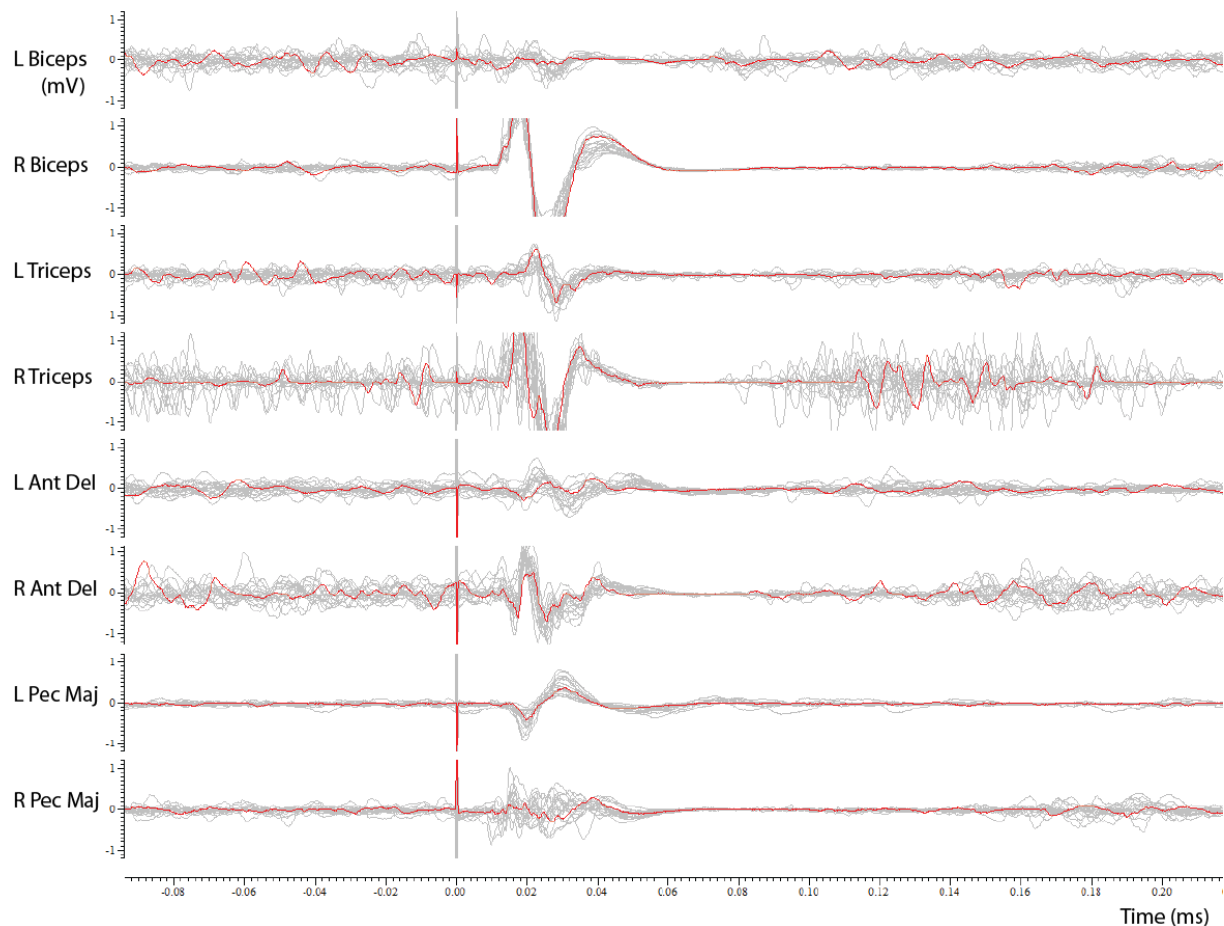


Figure 6.2 Example of MEP responses for subject TB31 (presenting with left hemiplegia) when stimulating the left hemisphere. Left sided responses represent ipsilateral activation (UI) when stimulating the unaffected hemisphere and right-sided responses contralateral activation (UC).

This procedure was repeated on day 6 to quantify changes induced by the 4 day training protocol. The same procedure was followed for both hemispheres. If a clear hotspot was evident, the train of stimulations was delivered at this site even if a different site was used before training. Alternatively the hotspot from the pre-training session was used for stimulations. 94 stimulations were delivered on the pre-training, as well as the post-training session (47 each hemisphere).

6.2.3. TMS analysis

For analysis measures of MEP latency, amplitude (peak to peak) and the number of responses recorded during the set of 20 stimulations at the identified hotspot were obtained. A response was defined as a MEP with a deflection of greater than 100 μ V (Swayne et al, 2008).

The training task in the robotic manipulandum required agonist activation of triceps, anterior deltoid and pectoralis major muscles. However, the reaching task to achieve muscle pre-activation additionally required eccentric activity of the biceps muscle. For completeness I include all 4 muscles to report TMS measures at baseline however biceps activity is not included when analysing change after training. Figures and analysis either specify which muscle is depicted or use a combined value of these muscles for group averages or a value for each of these muscles, i.e. in the scatterplot demonstrating correlations.

Measures were obtained using a customised script (Signal software, CEM) and each trace was visually inspected to verify correct identification of these events. The process of establishing each of the events is demonstrated in Figure 6.3.

Latencies were normalised on an individual basis to allow for inter-individual differences in peripheral conduction time (Eisen and Shtybel, 1990). Normalisation was performed by establishing the difference of the latency of the investigated pathway (UI and AC), in comparison to the latency of responses on the unaffected limb when stimulating the contralateral unaffected hemisphere (UC).

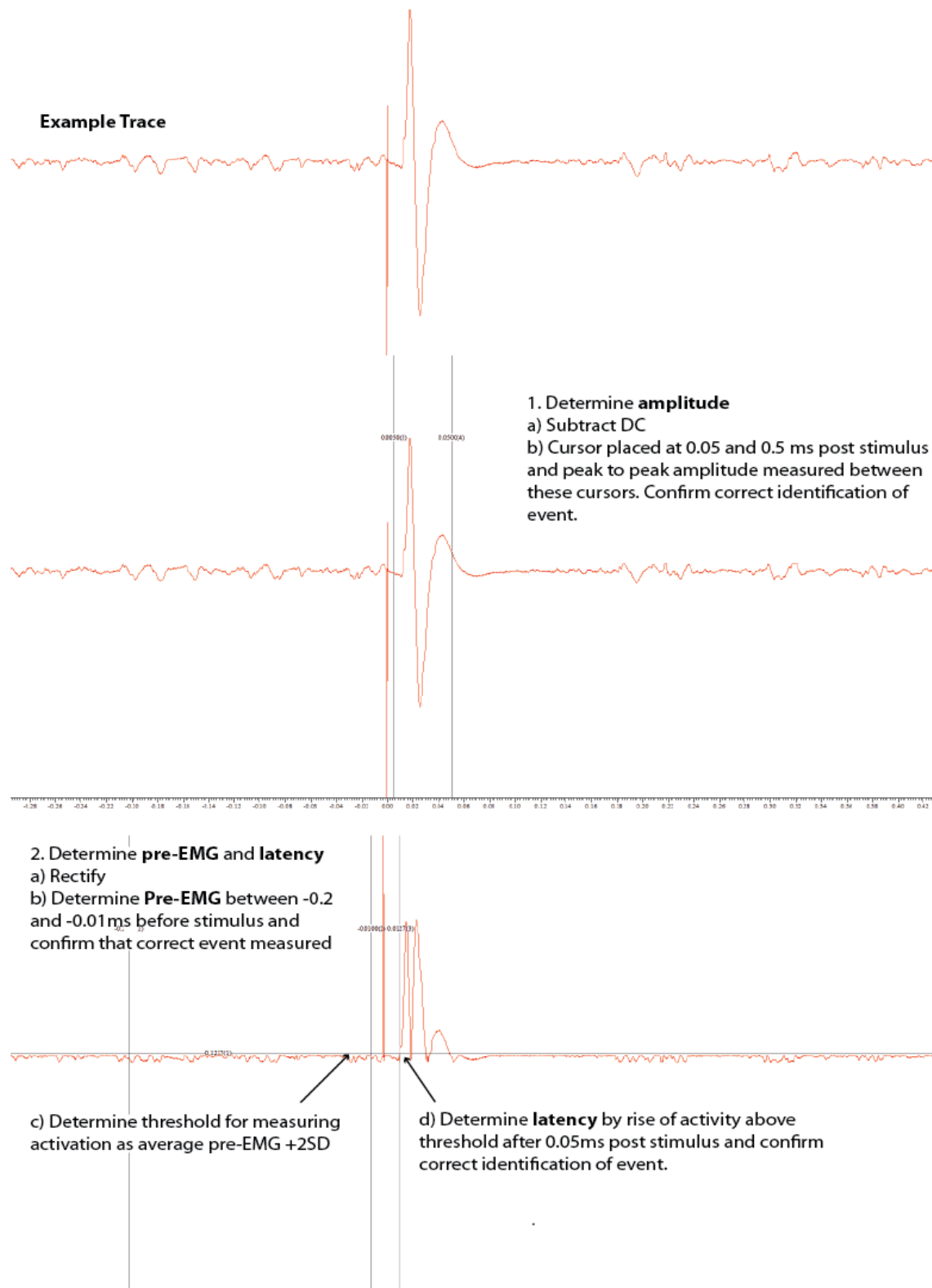


Figure 6.3. Process of determining MEP events with the use of a Signal script. 2 part process consisting of 1.) Subtracting DC followed by determination of peak-to-peak amplitude of MEP. 2.) determining latency by rectifying data, determining average pre-activation EMG and determining threshold to measure activation.

Additionally the laterality index (LI) was calculated. In this measure a laterality of 1 indicates complete contralateral control of limb movement, whereas LI= -1 indicates ipsilateral control (Schwerin et al., 2008). A response was defined as a MEP with a deflection of greater than 100µV (Swayne et al, 2008).

$$LI = \frac{\text{Responses contra} - \text{responses ipsi}}{\text{Responses contra} + \text{responses ipsi}}$$

Statistical analysis is performed as repeated measures ANOVA between biceps, triceps anterior deltoid and pectoralis major Muscle(4)*Path(2), indicating the pathways to the affected limb, either the contralateral pathway when stimulating the affected hemisphere (AC) or ipsilateral pathway stimulating the unaffected hemisphere (UI). Post hoc Student's t-test were performed when the ANOVA indicated significant differences in the data and Bonferroni corrections applied for tests involving multiple comparisons.

Spearman and Pearson's correlations are performed to assess correlations of Fugl-Meyer scores and baseline endpoint error respectively, with MEP measures on a subject-by-subject basis.

6.3. Results

This chapter aims to investigate the prevalence of contralateral and ipsilateral connections to proximal upper limb muscles in chronic stroke subjects. The affected and unaffected hemisphere was stimulated and features of the ipsilateral and contralateral MEPs are reported. 'Affected' and 'unaffected' refer to the respective hemisphere.

6.3.1. Participants

To investigate if the subgroup of individuals who received the TMS are representative of the whole study group we compared the improvements in endpoint error (Fig 6.4 A&B) as well as the reductions in movement speed variability (Fig 6.4 C&D) between the whole group (n=36) (results described in chapter 5) and the subgroup that received TMS (n=19).

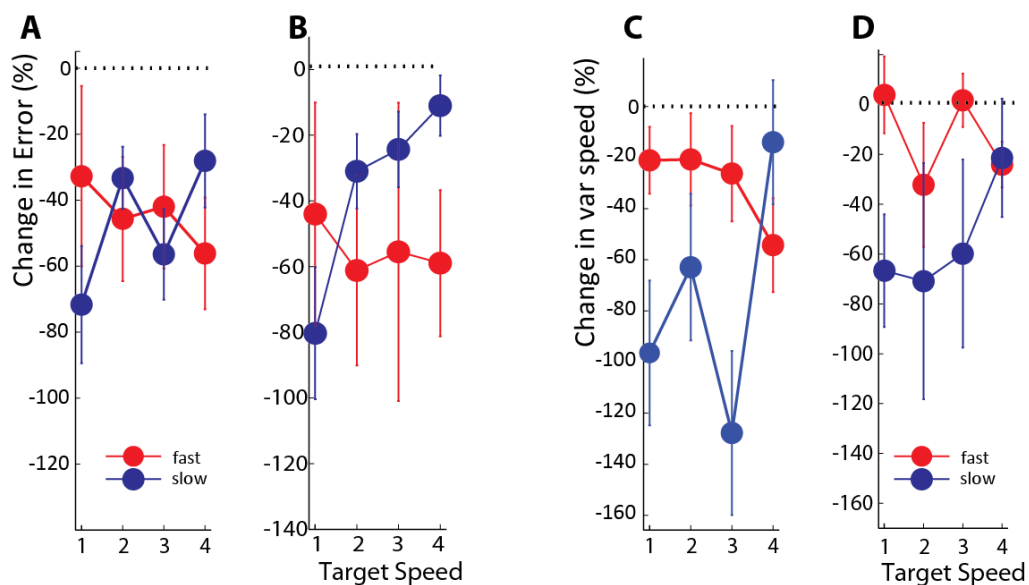


Figure 2.4 The reduction in endpoint error (expressed as percentage change) for the two training groups (blue=slow and red=fast) is compared between A) the whole study group (n=36) and B) the individuals of this study group who received TMS (n=19). The change in the variability of the maximum movement speed is compared for C) the whole study group and D) the individuals receiving TMS.

We can demonstrate that there was no statistical difference in the reduction of endpoint error for either the fast (effect of GROUP $F_{(1,27)}=0.381$; $p=0.542$) or the slow ($F_{(1,24)}=0.319$; $p=0.577$)

training group between the two set of individuals by the absence of an interaction in a 3wrmANOVA TargetSpeed(4)*TIME(2)*EXPERIMENT(2).

The reduction in maximum speed variability was also not different in the group of patients that received TMS (Fig 6.4 D) in comparison to the whole intervention group (Fig 6.4 C) in the fast ($F_{(1,27)}=0.858$; $p=0.363$) or slow ($F_{(1,24)}=3.419$; $p=0.077$) training group in the same analysis. We can therefore conclude that the subgroup of individuals receiving TMS can be assumed to be representative of the whole intervention group because the improvements observed are similar.

6.3.2. *Connectivity*

6.3.2.1. *Response frequency*

I measured the number of ipsilateral and contralateral responses, out of the set of 20 delivered to each hemisphere, observed at this stimulation setting. A response was defined as a MEP with amplitude of greater than 100 μ V. I thereby compared the number of responses in each pathway (PATH(4)-unaffected contralateral (UC), unaffected ipsilateral (UI), affected contralateral (AC), affected ipsilateral (AI)) and muscle (MUSCLE(4)) when stimulating the unaffected and affected hemisphere (Fig 6.5).

A clear difference can be observed between the different innervation paths (2wrmANOVA (MUSCLE(4)*PATH(4)), Interaction $F_{(9,27)}=3.779$, $p=0.003$). There was no statistical difference in the amount of responses observed in the different muscles nor did the difference in the responses in the other three pathways differ. Because there were no statistical differences between the different muscles the mean measure of all muscles was used for post-hoc t-tests, Bonferroni corrected for multiple comparison. Unsurprisingly the connection from the unaffected hemisphere to the contralateral unaffected limb was stronger than any of the other pathways (UC-UI, $t(18)= 12.960$, $p<=0.001$, UC-AC, $t(18)= 5.639$, $p<=0.001$, UC-AI, $t(18)= 8.997$, $p<=0.001$).

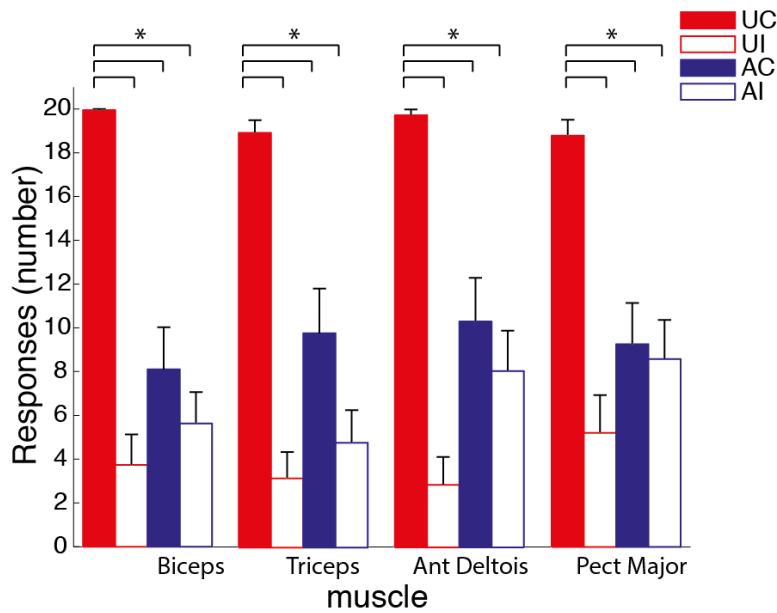


Figure 6.5. Response frequency for contralateral (filled) and ipsilateral (unfilled) upper limb muscles when stimulating unaffected (red) and affected (blue) hemisphere.

The two pathways of greatest interest are the pathways projecting to the affected limb; e.g. ipsilesional responses when stimulating the unaffected hemisphere (UI) and contralateral responses when stimulating the affected hemisphere (AC). I therefore compared the prevalence in these two pathways and although it appears that AC responses are more frequent than UI responses this was only approaching significance when performing a 2wrmanova (Muscle(4)*Path(2)-UI,AC) interaction($F_{(3,9)}=3.301$; $p=0.072$).

6.3.2.2. *Amplitude*

The same clear increased efficiency of UC pathways in comparison to the UI and AC pathways is evident when investigating the MEP amplitude (Fig 6.6). (Interaction in 2wrmanova Muscle(4)*Path(4) ($F_{(9,162)}=9.442$, $p<0.001$)). There was no difference of the strength of these connections between the different muscles and post-hoc t-tests again established the significant difference between the mean amplitude between the (UC-UI, $t(18)=9.269$, $p<0.001$, UC-AC, $t(18)=8.797$, $p<0.001$, UC-AI, $t(18)=9.007$, $p<0.001$) . However because we didn't standardise the amount of stimulation to the motor threshold nor controlled pre-activation EMG tightly we used the

number of responses as our measure of cortical excitability for further analysis rather than the amplitude of MEPs.

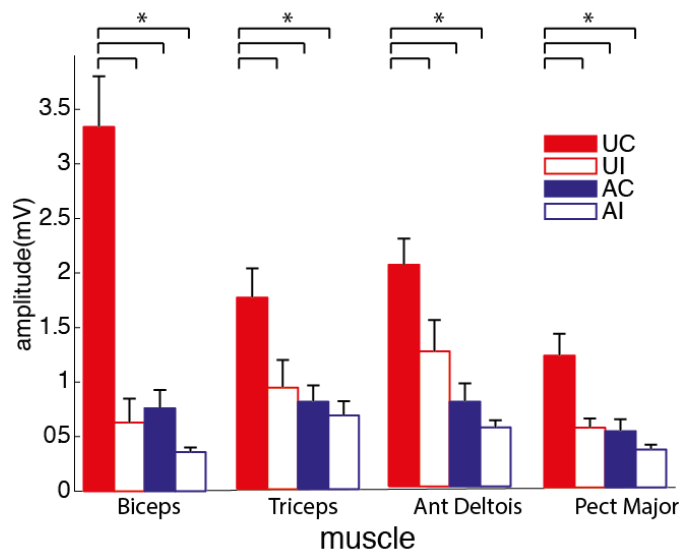


Figure 6.6. Mean MEP amplitude for contralateral (filled) and ipsilateral (unfilled) upper limb muscles when stimulating unaffected (red) and affected (blue) hemisphere.

6.3.2.3. Latency

I was interested to establish the timing of motor evoked potentials (MEPs) onset to investigate if the responses I could record were due to direct pathways or if the responses were delayed, potentially indicating indirect pathways with additional synapses. The latency of biceps brachii, triceps brachii, anterior deltoid head and horizontal pectoralis fibres were compared for contralateral and ipsilateral responses when stimulating the unaffected and affected hemisphere (Fig 6.7).

As expected, the latency for contralateral activation when stimulating the unaffected hemisphere was short in all investigated muscles and because there was no difference in the mean latency of the pathways we used the mean of muscle activity in each pathway (mean ((biceps+triceps+anterior deltoid+ pectoralis major)/4) = 11.7ms; (+/- 1.56)). The average latencies for UI (16.1ms; (+/- 3.62)) and both AC (16.1ms; (+/-2.57)) and AI(17.6ms; (+/-1.42)) were significantly longer

(2wrmANOVA (MUSCLE(4)*PATH(4), Interaction $F_{(9,27)}=6.564, p \leq 0.001$). There is no significant difference in the latencies in the different muscles but a significant difference between UC and UI ($p=0.023$) and between UC and AC ($p=0.050$) in Bonferroni corrected post-hoc t-tests.

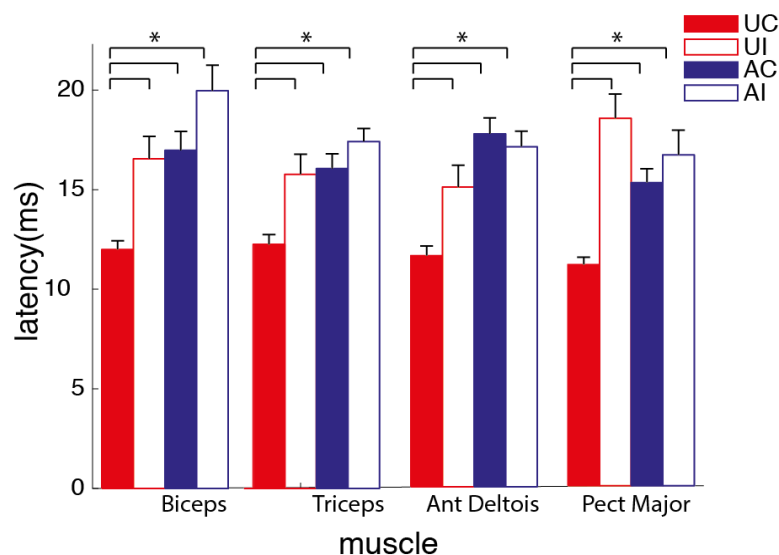


Figure 6.7. Latency of MEP onset for contralateral (filled) and ipsilateral (unfilled) upper limb muscles when stimulating unaffected (red) and affected (blue) hemisphere.

I can therefore conclude that the characteristic of the ipsilateral pathways from the unaffected (UI) and the affected (AI) hemisphere share similar MEP characteristics in these measures. The contralateral responses are however very different between the unaffected and the affected hemisphere. The characteristics of the contralateral responses when stimulating the affected hemisphere are similar to the ipsilateral responses from both hemispheres (UI and AI).

6.3.3. Correlation to Impairment

6.3.3.1. Responses

To investigate if the presence and strength of the respective pathways are related to functional ability I performed correlation analysis between the connectivity (no of responses to TMS in a train of 20 stimulations) with our measures of functional ability (Figure 6.8) (Fugl-Meyer and

baseline performance in the reaching task). We compared how the responses in the UI and AC pathway correlated with function.

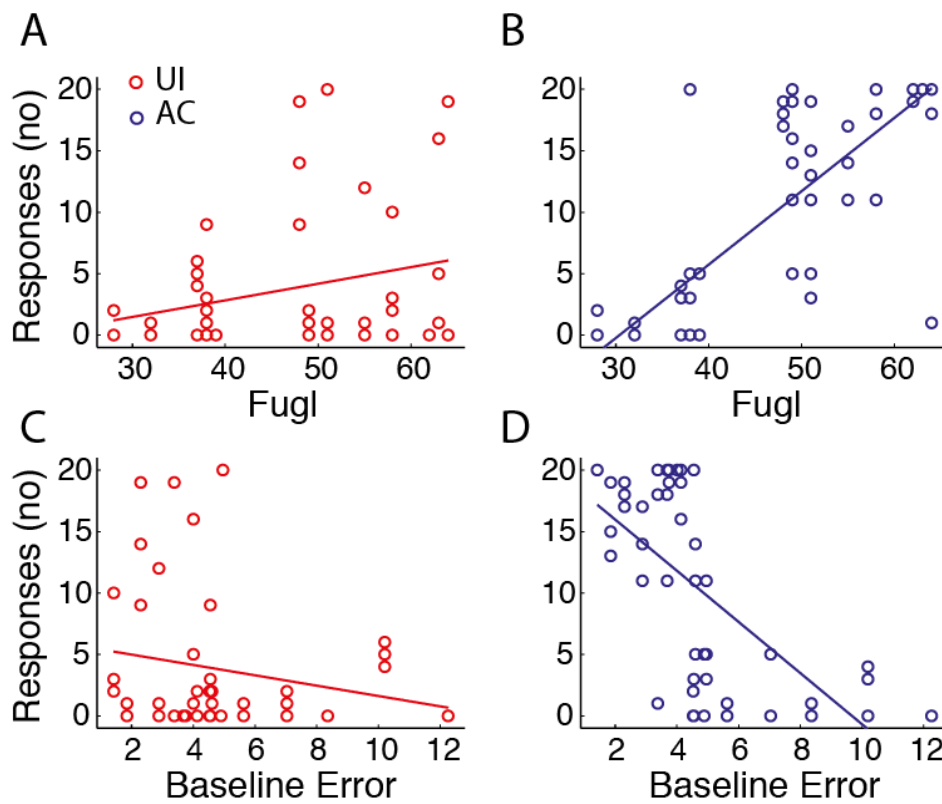


Figure 6.8. Correlation of Fugl-Meyer score with A) number of UI responses (red) and B) number of AC responses (blue), Correlation of baseline endpoint error with C) number of UI responses (red) and D) number of AC responses (blue). All data represents individual data points of traces from triceps, anterior deltoid and pectoralis major.

Ipsilateral responses to TMS stimulation of the unaffected hemisphere (UI) showed no linear relationship to measures of impairment (Fig 6.8A) (Fugl-Meyer score) ($\rho = .169$, $p = 0.373$) or baseline performance at the fast movement time (Fig 6.8C) ($r = .118$, $p = 0.535$). However contralateral responses to stimulation of the affected hemisphere were correlated with our measure of impairment (Fig 6.8B) (Fugl-Meyer score) ($\rho = .579$, $p < 0.001$) and strongly negatively correlated to the baseline error (Fig 6.8D) when performing the reaching task ($r = -.626$, $p < 0.001$). The two correlations of the Fugl-Meyer score with the respective pathway UI and AC differed significantly ($z = -$

2.167, $p=0.037$) as did the correlation between the baseline performance and the respective pathways ($z=4.00$, $p=0.001$).

6.3.3.2. Latency variability

I assessed the relationship between MEP latencies and the extent of ipsilateral (UI) or contralateral (AC) control of the affected side (Fig 6.9). To normalise the latencies between individuals I subtracted the individual mean UC latency for each muscle from the latency of the other 3 pathway latency. Therefore latencies are normalised on an individual basis, which accounts for differences in peripheral conduction time as a result of body height and age. I investigate if altered latencies in the UI and AC were correlated to good or poor motor function.

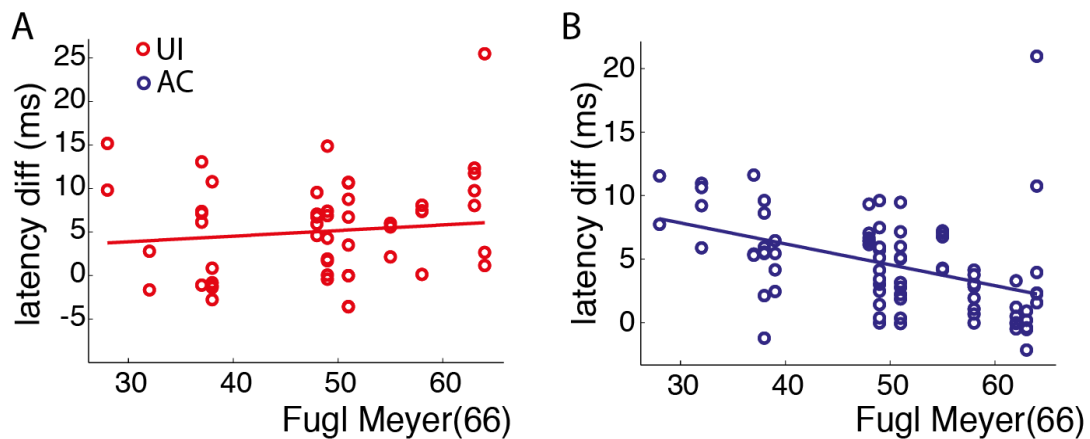


Figure 6.9. Correlation of Fugl-Meyer score with A) increased latency of UI responses (red) and B) increased latency of AC responses (blue) in relationship the UC response latency.

The UI and AC latencies are clearly increased in the majority of these individuals but show great inter-individual variation (Fig 6.9 A&B). In the UI there is however only a very limited correlation of the normalised latency to the Fugl-Meyer score (Fig 6.9A) ($\rho = .102$, $p = 0.532$). In contrast in the AC there is a clear negative linear relationship between the Fugl-Meyer score and the normalised MEP latencies (Fig 6.9B) ($\rho = -.455$, $p < 0.001$) indicating that individuals with shorter latencies have better functional ability. The correlations between the response latency and the two pathways (UI and AC) are significantly different ($z = 2.94$, $p = 0.0053$). Short latencies are probably an

indicator that corticospinal pathways are intact and that no extensive cortical remodelling occurred which would result in added synaptic connections, and thereby additional conduction time.

I can therefore show that greater excitability of the AC pathway (MEP responses), as well as maintenance of normal AC pathways latency, are predictors of functional ability. The number of UI responses is not related to impairment nor do they correlate with functional ability in this group of chronic stroke survivors.

6.3.4. Changes induced by training

I further wanted to investigate if our training paradigm induced any changes in the measure of corticospinal excitability and specifically if the training at fast and slow movement speed promote different mechanisms of recovery. For this analysis I did not include biceps activity because although this muscle was not active in our training protocol it was eccentrically activated during the TMS task. I observed small changes in the response incidence (Fig 6.10 A&B) and this raw data are used to calculate the laterality index (Fig 6.11). Delivering TMS to the unaffected hemisphere showed that the training groups differed in the amount of UI responses observed after training (2w rmANOVA (Time(2)*GROUP(2), effect of GROUP $F_{(1,55)}=5.377$; $p=0.024$), namely a reduced number of UI responses (Fig 6.10 A) for the slow training group ($t_{(26)} = 2.108$ $p = 0.045$). For contralateral responses when stimulating the affected hemisphere (AC)(Fig 6.10 B) an interaction was observed in a 2wrm ANOVA ($F_{(1,55)}=4.878$; $p=0.031$), but neither the increase in responses observed in the fast training group, nor the reduction for the slow training group was significant. This finding indicates that training at slow velocity reduces the corticospinal drive from the unaffected hemisphere. The two training protocols have opposite effects on the amount of crossed corticospinal drive from the affected hemisphere, however whether this is by increased drive after fast training or due to reduced reliance after slow training is inconclusive. No changes in response latency were observed in the affected upper limb after training with either ipsilateral or contralateral stimulation (Fig 6.10 C&D).

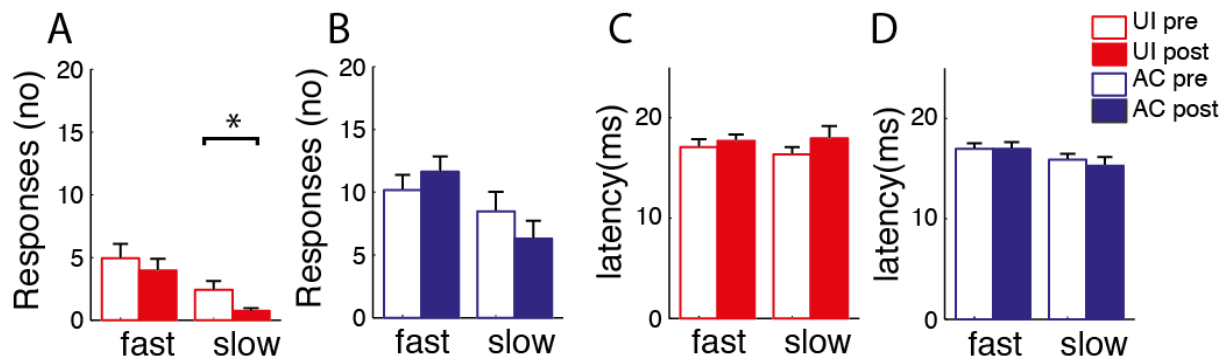


Figure 6.7. A-B) Change of MEP number of responses and C-D) latency before (unfilled) and after(filled) training for the two training groups (fast and slow). Red graphs depicts UI responses and blue graphs AC MEP responses.

When using the alterations in MEP prevalence reported in Fig 6.10 to calculate the laterality index (Schwerin et al., 2008) we did not find any significant changes in laterality for either of the training groups (Fig 6.11).

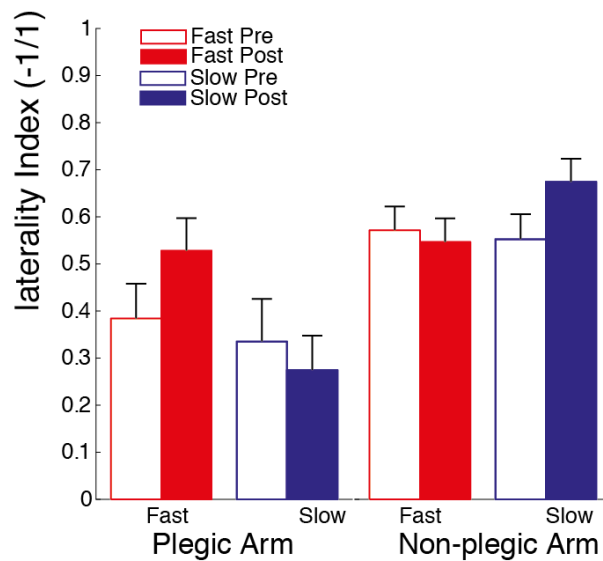


Figure 6.8. Laterality index before (unfilled) and after (filled) training when stimulating the unaffected (red) and affected (blue) hemisphere for the fast and slow training group.

6.4. Discussion

Transcranial magnetic stimulation can be used to investigate the integrity of corticospinal pathways after stroke (Turton et al., 1996, Bawa et al., 2004, Barker et al., 2012). In this set of experiments both hemispheres were stimulated and responses were measured in the contralateral and ipsilateral pathways. A standardized stimulation protocol of 70% MSO was used for all individuals. Only the stimulation site was tailored to each individual's hotspot for MEPs in the affected upper limb. Twenty stimulations were delivered to each hemisphere's hotspot and ipsilateral and contralateral responses were recorded. The number of stimulation was limited to maintain patient comfort and prevent activation fatigue.

In this set of results I can show that in our stroke patients the affected upper limb was activated by both contralateral connections from the affected hemisphere (AC) as well as, to a lesser degree, by ipsilateral connections from the unaffected hemisphere (UI). The responses from both UI and AC pathways had longer conduction time with large inter-individual variation. In this group of chronic stroke survivors the integrity of the contralateral corticospinal tract from the affected hemisphere was a strong predictor of functional ability. However ipsilateral MEP responses to TMS stimulation of the unaffected hemisphere did not correlate with functional ability.

6.4.1. *The pathways and their involvement in function*

The reduced size and number of MEP responses in the weak upper limb after contralateral stimulation and the increased prevalence of ipsilateral responses reproduce previous findings in stroke patients (Turton et al., 1996, Barker et al., 2012).

Responses to stimulation were measured in 4 pathways, the UC, UI, AC and AI. Latencies of contralateral MEPs when stimulating the unaffected hemisphere (UC) are short as expected in proximal pre-activated muscles (Rothwell et al., 1987, Bawa and Lemon, 1993, Kischka et al., 1993). In contrast, latencies in all other pathways were longer, replicating previous findings (Turton et al., 1996, Alagona et al., 2001, Schwerin et al., 2011, Barker et al., 2012).

Normalization of the latency to the UC latency allows an estimation of onset delay on a subject-by-subject basis while discounting inter-individual differences in peripheral conduction time due to height and age differences (Eisen and Shtybel, 1990). Longer conduction times, observed after stroke are thought to be an indicator of indirect pathways due to re-wiring and the incorporation of more synapses along the conduction path (Schwerin et al., 2008). In this patient population the latency of responses when stimulating the UI pathway was widely distributed. Surprisingly, in some individuals, the latency was the same as in the UC, which must indicate fast direct ipsilateral connections to the affected limb. This has been previously reported by Schwerin et al 2008, and in their study they also observed that MEP amplitudes were of the same size in the UI and UC responses in pectoralis major (Schwerin et al., 2008). The presence of this rapid connection is interesting and may be due to plastic unmasking of a non-excitabile pathway in healthy individuals. However, this pathway has now been largely dismissed as a contributor to functional recovery (Palmer et al., 1992, Ziemann et al., 1999) that may explain the poor correlation observed between the latency of the UI responses and functional ability. However the majority of response latencies in our stimulation paradigm were delayed to a similar magnitude as has been reported in stroke studies (Turton et al., 1996, Alagona et al., 2001) indicating indirect pathways, with potential additional synaptic connections. Contralateral response onset latencies, when stimulating the affected hemisphere were also variable. However in this pathway shorter latencies, and thereby probably intact corticospinal pathways are an indicator of better function. This finding supports previous studies that intact corticospinal pathways (Stinear et al., 2007) and more normal patterns of cortical activation (Ward et al., 2003) are predictors of good recovery.

In our stimulation paradigm stimulation was performed at an intensity of 70% MSO, rather than a tailored intensity in relation to each individuals motor threshold. This level of stimulation is not uncomfortable and thereby maintains patient compliance. Additionally a ceiling effect is unlikely to be observed in comparison to other stimulations paradigms where 90-100% MSO is used (Schwerin et al., 2008, Barker et al., 2012). In these paradigms stimulation intensity of over 150% motor

threshold can occur for more excitable pathways. However, a floor effect and absence of responses is possible in our intensity of stimulator setting.

The presence of MEP responses was used as the primary measure of excitability, rather than MEP amplitude (Misawa et al., 2008, Swayne et al., 2008). MEP amplitude is susceptible to alterations in the activation of the system which can be controlled by maintaining the same pre-activation EMG activity. For this method maximal EMG activity is measured prior to testing and pre-activation is performed at a percentage of this activity (Kischka et al., 1993, Bawa et al., 2004, MacKinnon et al., 2004). However, in this protocol I did not measure maximal EMG activity or standardize pre-activation as we measured MEPs in 4 different muscles in individuals with upper limb weakness. Stimulations were delivered using a footswitch to time stimulation with the period of maximal muscle activity during reaching. In proximal muscles, pre-activation is very important to elicit MEPs (Alagona et al., 2001, Bawa et al., 2004, Barker et al., 2012) but the metrics of MEP responses are not as sensitive to different levels of pre-activation muscle activity (Kischka et al., 1993, MacKinnon et al., 2004). Therefore the variation of pre-activation in this paradigm should not influence the incidence of MEPs within and between individuals and muscles.

A pre-determined MSO has been used in previous studies (Turton et al., 1996, Schwerin et al., 2008) and the response incidence is used when determining laterality (Schwerin et al., 2008). Interpreting changes in the laterality index is however difficult as they do not only indicate the changes in one pathway but additionally the alteration in the balance between the ipsilateral and contralateral connections.

The contribution of the contralateral and ipsilateral pathway to functional upper limb ability was investigated. The incidence of responses in the ipsilateral pathway was not correlated to either clinical impairment or the performance at our motor task at baseline. In previous studies greater incidence of ipsilateral responses were associated with poorer recovery, which our finding can not support (Turton et al., 1996, Alagona et al., 2001). However contralateral responses from the

lesioned hemisphere did predict both impairment as well as baseline task performance, supporting the importance of an intact crossed corticospinal tract for recovery.

6.4.2. Change due to training at two parameters

Previous studies have reported changes in MEP latencies due to training (Turton et al., 1996, Barker et al., 2012) and longitudinally in the recovery phase after stroke (Alagona et al., 2001), indicating improvements in performance and impairment. I did not observe any changes in latency in either of the training groups but in this very brief training protocol, latency changes would be surprising.

The change in the number of responses observed when stimulating the affected hemisphere, differentiating the two groups is interesting. In this paradigm accuracy improvements were required for both training groups however training was performed at either high or low velocity. This makes comparison to previous studies investigating either the frequency of movement (Jancke et al., 1998, Mattay and Weinberger, 1999) or varying accuracy demands (Winstein et al., 1997, Bueteifisch et al., 2014) difficult. However training at different movement speed imposes different demands on the system (Seidler et al., 2004, Shmuelof et al., 2014). Movements performed in the fast training group require explosive movements with high acceleration which has been found to be primarily reliant on the primary motor cortex (M1), the contralateral premotor areas and the basal ganglia (Karni et al., 1995, Desmurget and Grafton, 2000, Shmuelof et al., 2014) for specific skill learning paradigms (Hardwick et al., 2013, Shmuelof et al., 2014). In contrast the slow movement training probably incorporates a greater amount of feedback processes (Seidler et al., 2004), the cerebellum, thalamus, contralateral as well as ipsilateral sensorimotor cortex (Bueteifisch, 2014 #661 and potentially also a more cognitive strategy (Winstein et al., 1997, Bueteifisch et al., 2014). Changes in areas of the central nervous system, remote from M1 could explain the differential effect in contralateral activation in the slow training group. However the results of this study are not able to explore this finding further. A greater reliance on the ipsilateral hemisphere was not observed in the

slow training group but rather a reduction of excitability but again altered activation could be reliant on other areas than M1, the area we stimulated in this paradigm. Whether the main locus of the change observed with stimulation is cortical, spinal or even peripheral, is not clear (Hardwick et al., 2013).

In summary these findings support previous findings that intact corticospinal connections from the affected hemisphere are associated with good performance and recovery in this stroke population (Barker et al., 2012). Additionally there are two interesting findings. Firstly that training at fast and slow movement speed has differential effects on the response to transcranial magnetic stimulation of the affected hemisphere. This finding might be related to this specific training regime where we alleviate individuals' movement difficulties in an anti-gravity system. Ipsilateral projections might be more related to unsupported reaches involving functions of postural control. By supporting the arm we might preferentially target the CST and therefore see changes in AC projections when stimulating the M1. Secondly, UI responses are more common after stroke but they are not correlated to function. Why these ipsilateral pathways are up-regulated is therefore intriguing? Multiple studies show increased activity in remote brain regions, but their functional contribution to recovery has not been established (Bosnell et al., 2011, Bradnam et al., 2013). Recent studies in humans and in monkeys propose that these connections could be reticulospinal pathways and that they might contribute to functional recovery of the more severely affected individuals (Bradnam et al., 2011, Fisher et al., 2012, Zaaimi et al., 2012). In the chronic phase, as in our experiment, these pathways have been established and the functional contribution in more severely affected individuals is difficult to tease apart. Furthermore the evolution of these pathways after the stroke is not known (Misawa et al., 2008). However, during the acute period after stroke, when these pathways are up-regulated and potentially plastic (Dancause et al., 2005, Krakauer et al., 2012) interventions designed to harness these pathways might be functionally beneficial.

*7. EMG activation
patterns during reaching
in stroke*

7.1. Introduction

Functional limitations after stroke are caused by a host of impairments due to interrupted or altered corticospinal drive. Muscle weakness is a major contributing factor of limited function (Zackowski et al., 2004). However, muscle weakness and impaired muscle activation is not only due to a decreased ability to recruit motor units but also due to a number of other factors including an altered synchronisation of muscle activation (Dewald et al., 2001).

The temporal evolution of muscle activation especially in relation to agonist/antagonist pairs is altered after stroke (Wagner et al., 2007) and a reduction of muscle individuation can be observed frequently resulting in mass activation or co-contraction (Dewald et al., 1995, Levin, 1996, Chae et al., 2002). The balance of activity within force couples is at least as important for normal function as strength alone. The abnormal activation is typically manifested by coupling of elbow flexion with shoulder abduction, extension and rotation and to a lesser degree elbow extension with shoulder adduction-flexion and internal rotation (Twitchell, 1951, Beer et al., 1999). These alterations in muscle activity patterns have been shown to contribute to and are an indicator of motor impairment and difficulties in reaching (Milot et al., 2014). A further change in muscle activity patterns is observed when muscle activation of the weak muscle is saturated and additional muscles, not normally involved in the specific movement, are recruited in an attempt to overcome the inability to perform a task (McCrea et al., 2005).

Another contributing factor to alterations in the muscle synergy after stroke is a change to the involuntary stretch reflexes, manifested as spasticity (Pandyan et al., 2005). The effect of spasticity on functional impairments has not been demonstrated equivocally (Sorinola et al., 2009). Spasticity, measured as an increased stretch reflex during movement, has been shown to be correlated to impairment (Trumbower et al., 2010) although other studies maintain that spasticity does not influence reaching ability or performance (Gowland et al., 1992, Wilson et al., 1999, McCrea et al., 2005, Wagner et al., 2007).

Electromyography has been used to detect the alterations in muscle activity patterns due to stroke (Barker et al., 2009, Roh et al., 2013). During fast movements in healthy individuals, EMG activity occurs in a tri-phasic pattern consisting of an initial agonist burst for movement initiation, followed by an antagonist burst to brake the movement and a final agonist burst to assist in endpoint accuracy control (Basmajian, 1967). This pattern is disrupted after corticospinal damage (Gowland et al., 1992) and it has been proposed that changes in this pattern can be used as a marker of corticospinal damage and a measure of neural function, sensitive to change induced by rehabilitation (Ellis et al., 2005, Wagner et al., 2007, Barker et al., 2009, Safavynia et al., 2011, Cheung et al., 2012, Tropea et al., 2013). Changes induced by training can include earlier and greater initial activation of the agonist, increased ratio of the agonist/antagonist activation ratio, increased maximal activation and increase rate of force production (Aagaard et al., 2002, Wagner et al., 2007).

I here investigated if EMG activity patterns during the performance of the fast reaching task could be used to detect a number of features. 1.) I hypothesised that we would observe a disturbance in the temporal evolution of muscle activity and amount of muscle activity in regards to the triceps brachii to biceps brachii activation ratio. 2.) I further hypothesised that abnormal EMG activity could be used as a marker of impairment in this set of participants in the reach training paradigm. And 3.) I hypothesised that training performed at the fast movement speed would alter this pattern more than would be observed at slow movement speed training (Basmajian, 1967, Gabriel, 1997).

7.2. Materials and Methods

See chapter 3 for full details of patients sample and testing procedure.

7.2.1. Patient sample

Of the 37 participants in the reaching study 19 individuals were eligible for and agreed to have transcranial magnetic stimulation (TMS). This sample was investigated for corticospinal connectivity and additionally for the EMG activity during reaching movements. Inspection of data revealed missing traces in one individual and their data therefore had to be excluded from further analysis. The remaining sample consisted of two groups, 9 stroke survivors performing training at the fast movement speed and 9 at the slow movement speed. (See table 5.1).

7.2.2. EMG recording

EMG activity was measured during the testing day for both the affected and the unaffected upper limb. Sampling was performed while establishing movement accuracy at the fast movement speed. I only analyzed the activity during fast contractions because EMG signals have limited use in analyzing contractions of slow muscle fibers (Basmajian, 1967, Loeb, 1986) as confirmed in the very small signal size in our slow movement condition. The measurement was repeated for the affected upper limb on the post training test day. EMG activity was measured from 800ms before to 2200ms after movement onset. EMG activation was compared on a subject-by-subject basis between the affected and the unaffected arm or between pre and post-training activation profiles. Stroke patients also performed a set of reaches with their unaffected arm at their individually determined slow and fast movement speed, with EMG monitoring, to be used as control for the EMG traces of the affected upper limb.

EMG was recorded with self-adhesive AG/AgCl electrodes (Skintact®) placed over the muscle belly of bilateral biceps brachii, triceps brachii (lateral head). The electrodes were positioned in-line with the muscle fibres ~2cm apart after skin impedance was reduced by cleaning the skin and using an abrasive scrub (Nuprep Skin Prep Gel, Weaver and Company, USA) in accordance to SENIAM EMG recording recommendations (Hermens et al., 2000). Methods proposed by Kendall McCreary et al,

(Kendall McCreary et al., 2010) where followed to ensure correct electrode placement and verified by inspecting the EMG activity. The cathode was always placed proximally and the anode distally over the muscle belly (Loeb, 1986). The reference electrode was placed over the bony prominence of either the acromio-clavicular joint or the clavicle (Hermens et al., 2000).

EMG signals were amplified and filtered (20 Hz to 1kHz) with a D360 amplifier (Digitimer Limited Welwyn Garden City, UK). The signals were sampled at 5 kHz and digitised using a laboratory interface (Power 1401, Cambridge Electronics Design (CED), Cambridge, UK) and stored on a personal computer for display and off-line data analysis.

For muscle activation pattern analysis each sampling epoch was initiated by a digital output generated by the C++ program when reaching movement was initiated and consisted of a 3000ms sampling window, of which 800ms sampled the pre-activation period.

7.2.3. EMG analysis for muscle activation patterns

For muscle activation patterns I extracted the onset of muscle activity, mean rectified activity and maximum EMG amplitude (Aagaard et al., 2002) between the onset of muscle activity and the time when movement was terminated (activity offset). A custom written Signal Script was used to detect activity events and each trace was visually inspected to confirm correct identification of events.

The onset of EMG activity was defined as the time point when EMG activity increased to a level of two times the standard deviation of the baseline and the offset where the activity decreased below this level again after activation (Dewald et al., 1995).

There are limitations to the analysis we have performed here. The value of the EMG data could have been improved by recording and analysing EMG activity onset, offset and peak activity for each activity burst (Wickham and Brown, 2012). The relationship of these measures to the onset of reaching movement could have been determined by using a set threshold (i.e.10% of maximum

activation of movement or 2 SD of pre-activation EMG). The agonist (biceps) and antagonist (triceps) muscle events and how each of these phases relates to peak displacement, peak acceleration and peak velocity would provide insight into the tri-phasic activation and the relevance of each muscles contribution to the movement onset, performance and termination.

However a number of individuals presented with mass activation patterns where all muscles were activated together and no tri-phasic activity was observed (Example trace Fig 7.1).

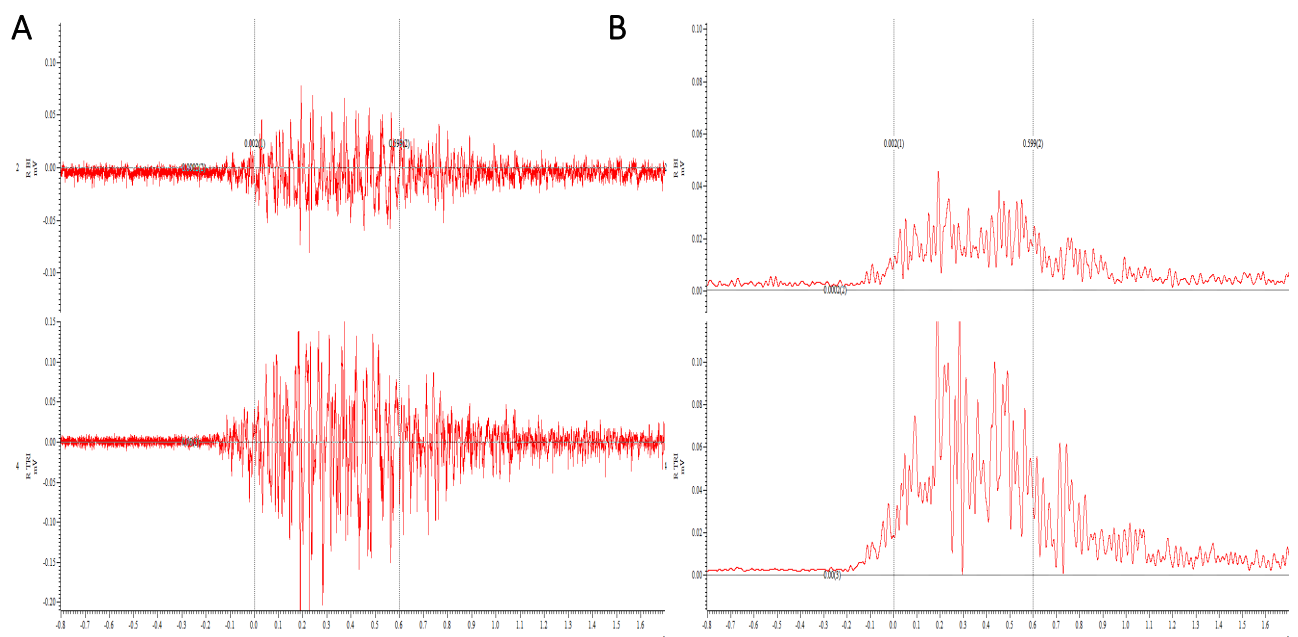


Figure 7.1. Example of a raw (A) and filtered (B) EMG data trace of a single movement demonstrating mass activation with no discernible tri-phasic activation. Vertical cursor at 0s indicates onset of movement and second cursor indicates end of movement limit.

Additionally a movement activity offset was difficult to detect in many individuals (Fig 7.2).

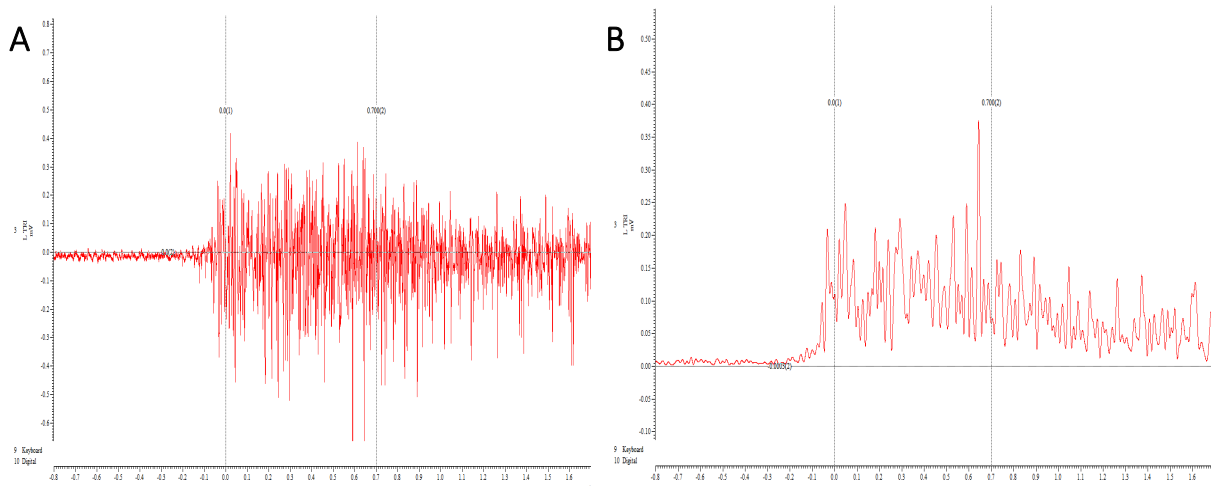


Figure 7.2. Example of a raw(A) and filtered(B) EMG data of a single reaching movement demonstrating no offset and triceps movement activity. Reaching movement started at 0s (cursor 1) and terminated before the movement limit set at 700ms (cursor 2) but triceps activity was sustained after the movement was completed.

Therefore the presence and alterations to tri-phasic activation patterns was not explored in this analysis. The main measure explored by the EMG analysis was to see if we could observe abnormalities in triceps and biceps activation, which would highlight mass-activation patterns as well as over-activity presumably due to spasticity. We further analysed the mean activation to establish the effect of training on this measure.

Additional parameters were computed to define the ratio between triceps and biceps activation and the relationship of maximal to mean biceps activation.

$$Ratio \left(\frac{Tri}{Bi} \right) = \frac{mean \ activity(mV)(triceps)}{mean \ activity(mV)(biceps)} \quad (Chae \ et \ al., \ 2002, \ Barker \ et \ al., \ 2009)$$

$$\frac{Max}{Mean(Bi)} = \frac{max \ Amplitude \ (mV)}{mean \ activity \ (mV)} \quad (Wagner \ et \ al., \ 2007, \ Barker \ et \ al., \ 2009)$$

Normality of distribution was assessed using Kolmogorov Smirnov test of homogeneity. In the case of non-normal distribution data were log transformed and this is reported in the text. Actual measures of muscle activity are depicted in the graphs.

Statistical analysis was performed by 2 way repeated measures ANOVA investigating the differences between the affected and unaffected (SIDE(2)) biceps and triceps muscle (MUSCLE(2)) activation . I also analyzed change of biceps and triceps activation patterns (Muscle(2)) due to training TIME(2) between the two training protocols (GROUP(2)) in a 3wrmanOVA. Correlation of muscle activation pattern with baseline performance and clinical impairment level was investigated on a subject-by-subject basis by Pearson's (for parametric measures) and Spearman correlations (for non-parametric; Fugl-Meyer scores) and the r- and rho-value and the significance are documented respectively.

7.3. Results

In this experiment I investigated the muscle activation patterns during baseline measurement of the supported 20cm reaching protocol at fast movement speeds. The reaches were performed with the affected as well as the unaffected upper limb and activation patterns are compared on a subject-by-subject basis.

7.3.1. EMG activity

Due to the confirmed muscle weakness in these participants, the mean rectified muscle activity as well as the peak activity levels for biceps brachii (Fig 7.3A) and triceps brachii (Fig 7.3B) were expected to be significantly lower in the weak affected upper limb, than in the unaffected limb. Interestingly, this was not the case and I could not demonstrate a difference between the activation in the unaffected and the affected side in a 2wrmanova (SIDE(2)*Muscle(2)). I did not observe an interaction however the mean activity was different between biceps and triceps demonstrated by an effect of MUSCLE ($F_{(1,17)}=31.244$, $p<0.001$) due to greater triceps activity in both the affected and the unaffected upper limb (Aff $t_{(17)}=-3.921$; $p=0.001$; UnAff $t_{(17)}=-4.991$, $p<0.001$), the movement agonist in this reaching movement.

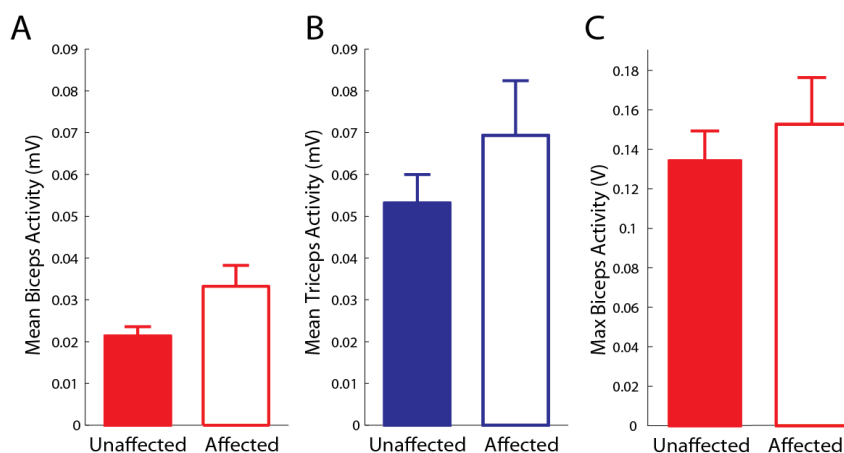


Figure 7.3. Mean rectified muscle activity for the unaffected (filled) and affected (unfilled) A) biceps (red) and B) triceps (blue) muscle during fast reaching movement at baseline. C) Maximum biceps activity.

I expected that the non-affected limb would have greater maximum biceps activity. This would mean that the high level of biceps activity observed in the affected upper limb was due to sustained activation and the activation on the unaffected side would be a short but stronger burst of activity. However when performing a 1wrmanOVA (Side(2)) on the maximum activity of biceps (Fig 7.3C), I did not observe a significant differences between SIDE.

Previous studies indicate that this increased muscle activity could be explained by poor individuation of distinct muscle patterns and mass activation of the upper limb and the antagonist biceps muscle (Twitchell, 1951, Zackowski et al., 2004). However when the amount of muscle activity was correlated with clinical impairment (measured by the Fugl-Meyer upper limb score) a weak positive correlation, approaching significance (Spearman's $\rho = .461$, $p = 0.054$), was observed (Fig 7.4). This finding does not support the theory that the amount of activity is due to mass activation, which would interfere with functional activities.

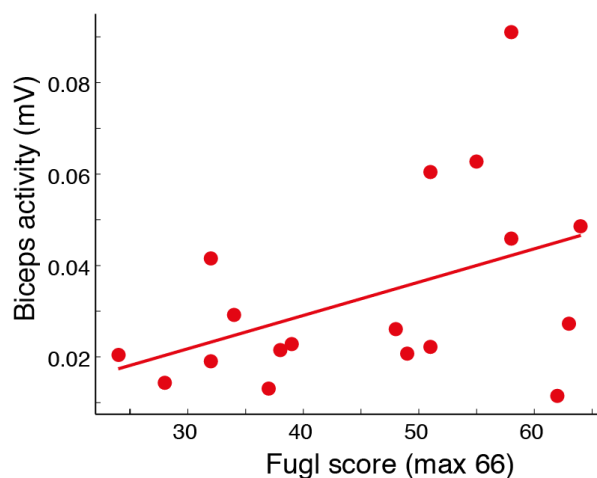


Figure 7.4. Correlation of Fugl-Meyer score with mean biceps activity during reaching movement at baseline assessment.

7.3.2. *Movement onset*

To investigate if the temporal evolution of muscle activation can demonstrate poor muscle activation patterns due to co-contraction I determined the onset of biceps and triceps muscle activation in relation to movement initiation. The onset of muscle activity was established for biceps

brachii (Fig 7.5A) and triceps brachii (Fig 7.5B) and the timing was compared between the affected and the unaffected upper limb. The time of onset for biceps brachii was variable with large standard error. In a 2wrmanOVA(Muscle(2)*SIDE(2), I observed an effect of Muscle ($F_{(1,17)}=36.022$; $p\leq 0.001$) due to the clear differences between the biceps and triceps activity onset (Aff $t_{(17)}= 5.994$; $p\leq 0.001$; UnAff $t_{(17)}=3.243$; $p=0.005$) but I did not observe an interaction or an effect of SIDE. The apparent delayed onset for biceps activity onset (Fig 7.5A) in the affected arm was not significant nor was the difference in triceps activation (Fig 7.5B).

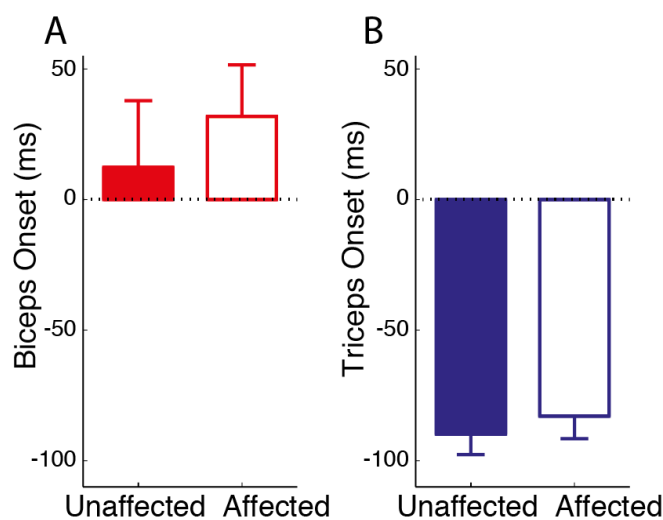


Figure 7.5. Onset of muscle activity in relation to movement onset for unaffected (filled) and affected (unfilled) upper limb for A) biceps (red) and B) triceps (blue) muscle at baseline assessment.

Although the delayed onset of biceps activity was not statistically significant I wanted to investigate the relationship of altered activation timing on baseline performance and impairment on an individual basis. A well-timed antagonist biceps burst of activity should be late in the movement whereas co-contraction would be indicated by early activation. In keeping with this theory I could show a negative correlation of biceps activity onset and baseline performance (Fig 7.6A&B). Individuals with later onset of biceps activity had smaller endpoint errors, both when moving at slow (Fig. 7.6A)(Pearson's correlation $r=.5097$ $p=0.0307$) as well as at fast (Fig 7.6B) movement speeds (Pearson's correlation $r=.5139$ $p=0.0292$). When the outlier of very large baseline error were

removed a significant correlation remained at the fast movement speed ($r=.562$ $p=0.0188$) but for the slow movement it was no longer evident ($r=.4927$ $p=0.0852$). Interestingly biceps activity onset did not correlate to the Fugl Meyer score (Fig 7.6C) (Spearman's $\rho=.195$, $p=0.437$). The delayed onset of triceps activity in the affected upper limb did not show any correlation with impairment.

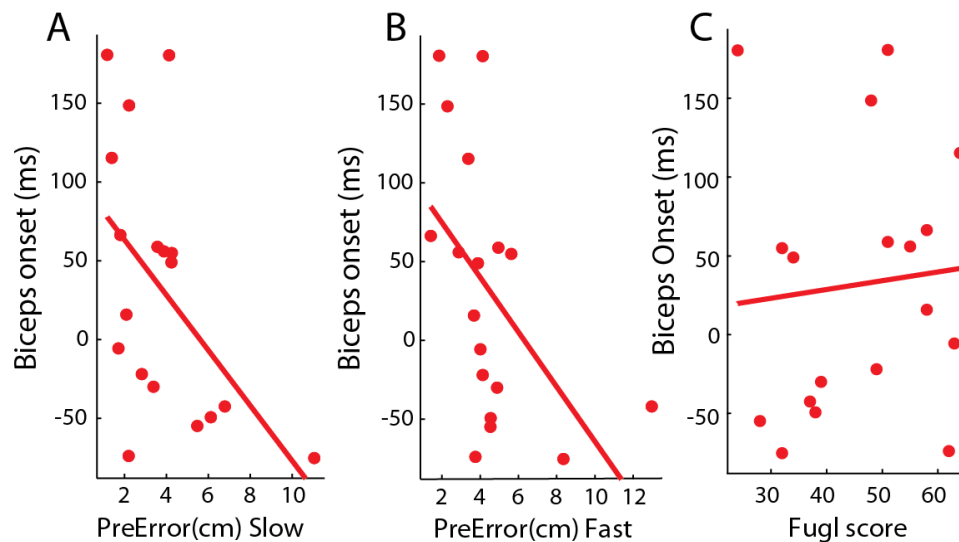


Figure 7.6. Correlation of baseline endpoint error with onset of biceps activity at A) slow and B) fast target speed and C) with Fugl-Meyer score

7.3.3. Ratio of Agonist to Antagonist activity

Difficulties of muscle activation patterns and poor modulation between agonist to antagonist activity can be detected in the ratio of activity in these muscle pairs. The activity levels were not correlated in the unaffected upper limb (Fig 7.7A) (Pearson's correlation; $r=.2668$ $p=0.2845$) however in the affected upper limb (Fig 7.7B) there was a strong correlation (Pearson's Correlation; $r=.7312$, $p=0.0006$). For this set of subjects the ratio (Fig 7.7C) of triceps to biceps activity for the unaffected (mean=3.04, (+/- 2.06)) and affected (mean 2.38; (+/-1.35)) limb was however, not significantly different.

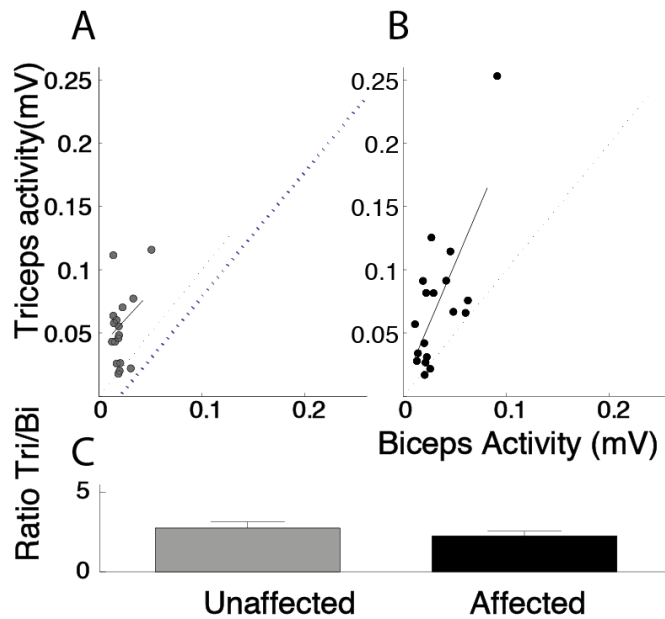


Figure 7.7. Correlation of A) unaffected (grey) and B) affected (black) mean biceps to triceps activity and C) muscle activity ratio of triceps to biceps activity for the unaffected and affected upper limb.

Increased EMG activity in the initial portion of movement demonstrates better recruitment of muscle fibers and a better ability to generate muscle power (Aagaard et al., 2002). The 50ms preceding movement activation and the 100ms after initiation of movement are also seen as the feed-forward portion of a movement, in which the movement observed is a representation of the motor command as feedback processes are too slow to alter this period (Shadmehr and Wise, 2005).

I therefore repeated the analysis performed above to see if poor activation could be observed in this initial portion of movement generation. A similar but even larger ratio of muscle activation can be observed as in the analysis of the whole movement (Fig 7.8). There is a close relationship between the amount of triceps and biceps activity as indicated by good correlations for both the unaffected (Fig 7.8A) (Pearson's correlation $r = .7219$; $p = 0.0007$) as well as the affected (Fig 7.8B) upper limb (Pearson's correlation $r = .7849$; $p = 0.0001$) but there is no difference in the magnitude of the ratio between the groups (Fig 7.8C). This shows that the initial recruitment of the

triceps muscle in relationship to the biceps was not different in the affected limb in the EMG measurements in our patient population.

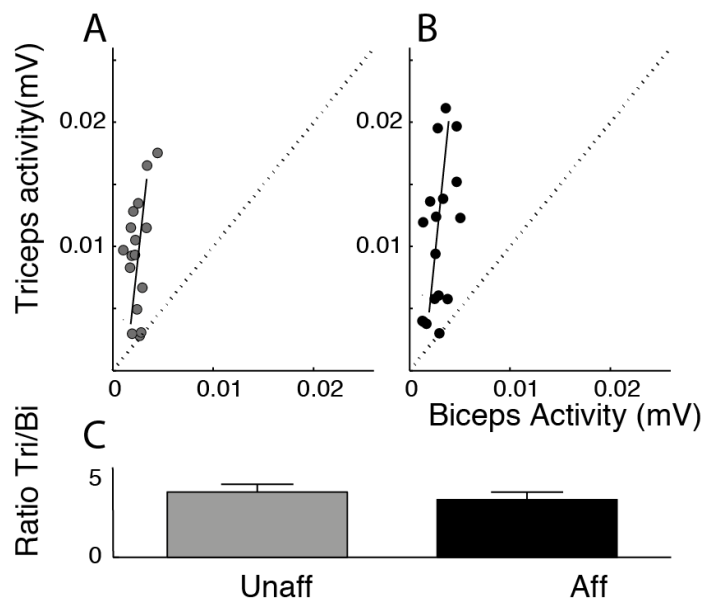


Figure 7.8. Correlation of A) unaffected (grey) and B) affected (black) mean biceps to triceps activity for the period from 50ms before movement onset to 100ms after movement onset. C) Muscle activity ratio of triceps to biceps activity for the unaffected (grey) and affected (black) upper limb for the activation period of 50ms before movement onset to 100ms after onset.

7.3.4. EMG changes due to training

I further analyzed whether training altered the onset of muscle activity and specifically the effect of training at fast and at slow movement speed (Fig 7.9) in a 3wrMANOVA (MUSCLE(2)*TIME(2)*GROUP(2)). A trend to an interaction ($F_{(1,16)}=4.322$, $p=0.054$) demonstrates that the two training speeds had differential effects on the onset of muscle activity. Muscle activity onset was changed by training (Effect of TIME, $F_{(1,16)}=54.716$, $p<0.001$) and differed in biceps and triceps (Time*Muscle($F_{(1,16)}=4.464$, $p=0.051$)).

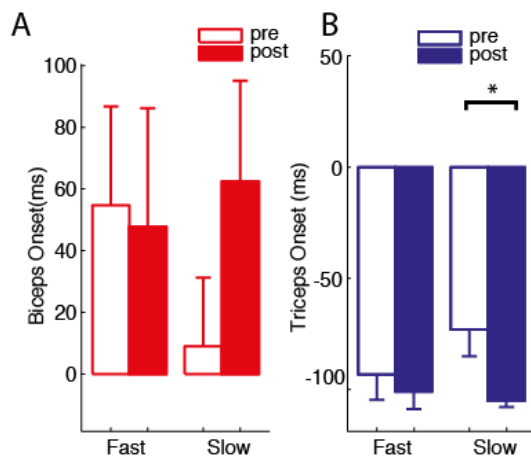


Figure 7.9. Onset of EMG activity of affected upper limb before (unfilled) and after (filled) training for fast and slow training group for A) biceps (red) and B) triceps (blue) muscle.

7.3.5. Antagonist activation

Spasticity is a common symptom after stroke and in this paradigm fast reaching movements could elicit spasticity of the antagonist, biceps muscle. To establish if training at either fast or slow movement velocity resulted in alterations of hypertonus I establish individual mean biceps activity and the maximum activation of the muscle. I propose that in this fast reaching movement, biceps spasticity can be demonstrated as a spastic catch by the maximal activity during the reaching movement. I analyses how the mean (Fig 7.10A) and the maximum (Fig 7.10B) activity changed in the two training groups due to training and if this differed depending on the training performed with a 3wrmANOVA (ACTIVITY(2)*TIME(2)*GROUP(2)). The effect of the training protocol was not different as there was no interaction. I can thereby conclude that the maximum EMG activity, a potential measure of biceps spasticity, did not change due to the training protocols, nor did the amount of EMG activity.

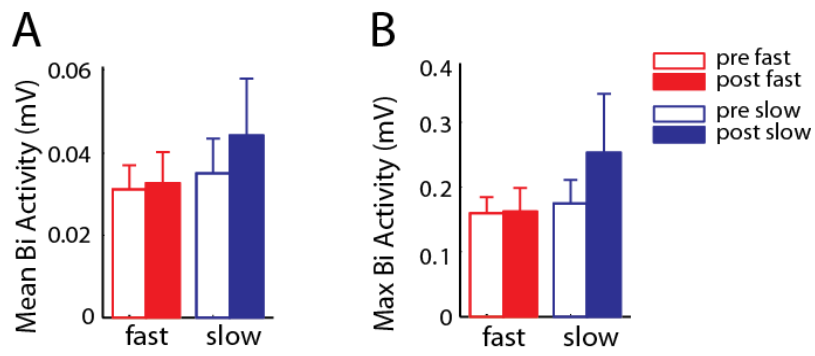


Figure 7.10. A) Mean biceps activity before (unfilled) and after (filled) training for the fast (red) and slow (blue) training group B) Maximum biceps activity.

7.4. Discussion

In this supported reaching paradigm, the onset and mean rectified activity of biceps and triceps muscles was sampled during fast reaching movements of the affected and the unaffected hand in a robotic manipulandum. EMG measurements of the affected upper limb were repeated after a week of intensive training, practising reaching accuracy at either slow or fast movement speed.

This paradigm of supported reaches in the manipulandum, not allowing compensatory strategies, require the same movements in the affected and unaffected upper limb. Muscle activity is controlled for movement velocity, movement extent as well as movement direction. It is therefore maybe not that surprising that the muscle activation patterns in terms of activation onset, mean and maximum activity for this set of stroke patients, were very similar between the affected and unaffected upper limb. Training resulted in very little alterations in biceps and triceps muscle activation. The similarity of activation patterns observed between the affected and unaffected limb, mirror findings of other experiments using unconstrained reaching movements (Barker et al., 2009, Cheung et al., 2009, Coscia et al., 2014) in comparison to the altered synergies observed in isometric force matching protocols (Dewald et al., 1995, Roh et al., 2013) and more sophisticated measures of synergy composition (Cheung et al., 2012, Safavynia and Ting, 2012).

7.4.1. Muscle activation levels, patterns and agonist-antagonist ratios

After stroke movement quality is compromised and individuals tend to move in stereotypical movement patterns, also called synergies (Twitchell, 1951). Reduced individuation impacts on functional ability of not only the distal (Lawrence and Kuypers, 1968) but also the proximal upper limb (Zackowski et al., 2004). A weakness in our study design and analysis is that the affected limb's activation pattern is compared to the activation observed in the unaffected limb. To control for intra-individual comparison of reaching movements and varying movement speeds depending on the ability of the affected hand, we compared activation between the affected and unaffected arm

intra-individually. This provides benefits of comparable joint-torques and body composition. However it has been clearly established that movement of the ipsilesional limb is also affected after stroke (Desrosiers et al., 1996). This comparison might partly explain the absence of abnormal activation patterns observed here however, the normalisation of movement achieved by de-weighting the arm has been also reported (Coscia et al., 2014).

Contrary to expectation I could not detect clear differences between muscle action of the affected and unaffected biceps and triceps muscles in our group of stroke patients while performing supported reaches. The muscle activation level and pattern between biceps brachii and triceps brachii during reaching were very similar in comparison to the unaffected upper limb. I assessed the synergy as the mean muscle activity, the onset of activity in relation to movement initiation as well as the mean activity ratio between the agonist and antagonist for the whole movement and the initial part of the movement as performed in previous studies (Wagner et al., 2007, Barker et al., 2009). The preservation of muscle synergies has been reported in a number of previous studies (Gowland et al., 1992, Wagner et al., 2007, Barker et al., 2009), however measuring muscle synergy solely by the timing of muscle activity onset and the ratio of activity, as performed in our analysis, has clear limitations. Muscle synergies during fast movements comprise triphasic activation of the agonist and antagonist and changes to the timing of these events are more informative of alterations of muscle activation patterns than onset and mean activation alone (Gowland et al., 1992). Analysis of abnormal activation patterns observed after stroke has been shown to be achievable by factor analysis measuring not only muscle activity interplay within specific synergies but also the number of observed synergies during movements (Cheung et al., 2012). However, the analysis in this chapter did not comprise these techniques.

Altered muscle synergies due to co-contraction have been demonstrated in isometric force matching protocols (Dewald et al., 1995, Roh et al., 2013). Co-contraction in these activities involve recruitment of additional muscles to perform an action, consistent with evidence that compensatory

strategies are used if task completion is difficult (McCrea et al., 2005). With greater functional impairment co-contractions increases in these tasks but also in unrestrained reaching tasks where alterations in EMG patterns have been observed in individuals with very low Fugl-Meyer scores (Cheung et al., 2009).

How these activation patterns are maintained despite stereotypical movement patterns observed in functional tasks is not clear. On a mechanistic level it has to be considered that moving and training in anti-gravity environments reduces the difficulty of the task significantly. Activation patterns of stroke individuals moving in supported environments and thereby the muscle synergies have been shown to be not significantly different to normal activation patterns (Coscia et al., 2014). Therefore the inclusion criteria in our set of patients is set to recruit a patient group who can perform this reaching task if gravity is eliminated. The task does not allow compensatory movements and therefore muscle activation patterns need to, and from this analyses appear to be maintained to a large extent.

7.4.2. EMG as a marker of impairment

I wanted to establish if the EMG activation patterns in our stroke patients could be used to detect neural function and disruption in descending control (Safavynia et al., 2011, Cheung et al., 2012). It is well established that interruption of corticospinal pathways lead to impairment (Stinear et al., 2007) and possibly greater dependence on remaining intact pathways, including brainstem pathways (Zaaimi et al., 2012). The projections of these brainstem pathways onto motoneurons are far less divergent than projections of the corticospinal tract (Matsuyama et al., 1997) and stereotypical synergies are therefore observed after lesions in animal models (Zaaimi et al., 2012). The stereotypical movement patterns and mass activation after stroke, could therefore be also due to a reliance on these remaining brainstem pathways. In this group of stroke patients I however did not observe abnormal movement patterns in our measures of activation in the supported reaching movement. EMG activation was abnormal and a triphasic recruitment pattern was not consistently

observed however, this finding was not further explored in this analysis. The other indication for EMG as marker of impairment was that on an inter-individual basis, very early activation of biceps correlated with poor task performance at slow and fast velocity, resulting in very large endpoint errors.

7.4.3. Effect of training on EMG activity

Various outcome measures are used to measure functional ability and change due to an intervention. Safavynia et al, found that EMG is sensitive and responsive enough to detect changes in muscle activity due to rehabilitation (Safavynia et al., 2011) and other studies report that training can alter muscle activation patterns (Ellis et al., 2005, Tropea et al., 2013). I wanted to establish how training at the two training velocities altered muscle activation profiles. I further wanted to investigate if alterations in the activation pattern could provide evidence that training at a fast movement speed resulting in greater changes in the feed-forward motor plan in comparison to slow movement speed training.

However the small changes in EMG activity I observed can not explain the change observed in performance in the training task. Training had very little effect on activation patterns and training at either slow or fast speed didn't alter our measures of activation. A number of factors might explain the lack of translation of the performance improvements to EMG measures. Firstly, the measures of EMG activation patterns used here are far less refined than in mathematical approaches using factor analysis investigating changes in the number and structure of muscle synergies after stroke (Cheung et al., 2009, Cheung et al., 2012). The computational analysis used in these approaches enables a far more detailed analysis of activation and thereby insights into changes in neural control (d'Avella et al., 2008, Safavynia et al., 2011, Cheung et al., 2012). Secondly our training protocol was very brief, only 4 days. Whether performance changes induced by this short training protocol result in significant changes of a variable measure, like EMG, probably depends on the resolution of measurement (McCrea et al., 2005). Because of the heterogeneity of recovery

mechanisms in stroke survivors, group analysis of alteration in EMG activation can fail to detect changes (Tropea et al., 2013). Improvements in accuracy for both training groups can be achieved by a variety of factors including improved recruitment rate of muscle fibres as well as increased muscle activity, which could both improve reaching accuracy (Gowland et al., 1992, Barker et al., 2009). In this chapter I have analysed changes to both of these measures but did not observe any clear change induced by training. However multiple other factors could also improve endpoint accuracy. Tri-phasic activation pattern could change in relation to the evolution and co-ordination of activation of the agonist and antagonist activity, alteration of timing of activity burst and earlier termination of movement with increased emphasis on endpoint control (Barker et al., 2009). Another possibility could be that this paradigm emphasising accuracy actually reinforces repeatability of a movement rather than an alteration in the motor command. However, these measures are not captured in our data analysis as explained in the methods section of this chapter and we therefore probably lack the sensitivity to detect changes in our measures. That being said, the use of supported movements does normalise movements and has in previous experiments shown not to show alteration that are seen in unsupported movements (Lum et al., 2004a).

Biceps spasticity is a common presentation after stroke and is known to be exaggerated by increased velocity (Pandyan et al., 2005). However exposure to repeated muscle activity has been reported to reduce spasticity (Schmit et al., 2000) and in line with these findings, the fast training group has a significant reduction in the modified Ashworth scale, a measure of stiffness, after training. The continual exposure to fast movements that the individuals in the fast training group were exposed to in this training paradigm did however not alter the maximum biceps activity, which could be an indicator of biceps spasticity.

A further line of investigation that could have been interesting would be to differentiate how the difference in activation patterns between individuals (tri-phasic, aspects of tri-phasic or mass-

activation), relates to TMS responses observed when stimulating different pathways but because we decided to only measure mean activation this analysis was not explored in the thesis.

EMG has been used to assess alterations in muscle activation patterns but interpretation of this noisy multi-faceted signal is known to be difficult (McCrea et al., 2005). I here investigated the pattern of EMG activation during fast supported reaches and the effect that 4 days of training had on these patterns. I found a surprisingly similar amount and pattern of muscle activation between the affected and the unaffected arm and training did not result in significant changes that could show a training effect nor a difference between the two training groups.

8. Conclusion

8.1. Summary

In this thesis I present two studies investigating the influence of training at either slow or fast movement speed on motor learning. One study investigates this learning in healthy individuals and one in individuals affected by stroke.

Chapter 4 demonstrates that in healthy individuals training speed influences the choice of movement speed after the training and thereby forms a habitual movement speed. Training at both fast and slow movement speed show training speed specific improvements in accuracy.

Chapter 5 shows that chronic stroke patients are able to improve at this task which does not allow compensatory strategies. Training at slow as well as at fast movement speed results in training speed specific improvements. Sensory impairment reduces learning and spasticity and muscle weakness influence baseline performance. Spasticity is not increased by training at fast movement speed.

Chapter 6 shows that in our group of stroke patients the presence and normal latency of corticospinal connections from the affected hemisphere to the affected limb predict functional ability. Training at fast and slow movement speed had differential effects on the incidence of MEP responses in the affected upper limb when stimulating the contralateral hemisphere.

Chapter 7 demonstrates that in this supported reaching paradigm EMG patterns for the chronic stroke patients are not abnormal and very little evidence of stereotypical activation patterns are observed.

In summary this thesis shows that chronic stroke patients can improve their performance in this reaching task with intensive practice, however, the accuracy improvements do not transfer broadly to non-trained movement speeds. Training at fast movement speed is not detrimental to stroke patients and spasticity is not increased.

The central messages are:

- The movement speed during training influences the choice of movement speed after the training. The clinical implication is that as training regimes tend to be performed with an emphasis on movement accuracy at slow movement speed, the slowness of movement observed in individuals after neurological event as well as in healthy ageing is reinforced. However motor tasks in daily life require alterations in movement speed depending on the accuracy requirements as well as task urgency (Fitts, 1954). Inclusion of fast movements during rehabilitation programmes would prevent reinforcing slowing of movement.
- The improvements in movement accuracy were training speed specific and didn't generalise broadly to other movement speeds. These local improvements indicate that the learning mechanisms at the two different speeds are different. Our results can only propose that this could be due to better integration of feedback in the slow training group and in the fast training group an improved ability to predict altered limb dynamics at fast velocities and resultant alterations of the feed forward command. Both movement speeds are clearly important in daily life and the two different learning mechanisms are probably important as well.
- Fast movement in the training protocol were not detrimental to individuals affected by stroke and did not increase spasticity. The two training protocols, slow as well as fast movement, were equally effective at improving endpoint accuracy although. However a distinct difference between moving at slow and at fast movement speed is that moving at higher velocity is more effortful (Newton's II Law of Motion, (Newton, 1687)). Therefore including fast movement in training regimes will on its own increase the force required during the training, a property of training regimes that is difficult to achieve in the rehabilitation setting (Lang et al., 2009).

8.2. Future Research

It would be interesting to further explore the influence of movement velocity during training, on motor learning within these broad categories.

- Investigating the optimal regime to incorporate different movement velocities
- Establishing the mechanical difference imposed by slow and fast movement
- Investigating the influence of fast and slow movements on hypertonus and spasticity.
- Studying the influence of training velocity in the acute/sub-acute phase after stroke
- Studying the relationship between neuroplasticity inducing protocols and different movement velocities during training

8.2.1. Optimal training regime

This pilot study investigated the effect of 4 days of training at either fast or slow movement speed. This is a very brief training period and normal rehabilitation regimes comprise of between 3-6 weeks of daily practice. It would therefore be beneficial to investigate changes in primary and secondary outcome measures for training regimes of 10-20 one hour sessions.

In this study the participants performed the training either only at slow or only at fast movement speed because I was interested how movement at fast movement speeds influenced learning and spasticity. However it is recognised that it is better if training to perform distributed practice, involving a variable training structure (Shea and Kohl, 1991). Mixed practice does not lead to greater amount of learning but crucially it results in better retention. Therefore a trial investigating the effectiveness of a training schedule including different movement speeds would be a worthwhile follow-up study to this project

8.2.2. Mechanical difference imposed by movement speed

The incomplete generalisation to non-trained movement speed indicates that the two movement speeds impose inherently different demands onto the system. In my analysis I can only

speculate that the difference is due to a reliance on feedforward learning in the slow group and a better motor plan due to feedforward learning in the fast training group.

It would be interesting to perform a study to tease apart the differences between these paradigms. Interaction torques at the shoulder and elbow joints should be calculated and analyses could investigate the effect of training at the two movement speeds on compensation for these torques (Sukal-Moulton et al., 2014). Feedforward learning will be evident in a reduction in the variability of the initial movement performance, while feedback integration would alter the later aspect of the movement (Shadmehr and Wise, 2005).

8.2.3. Investigating the influence of fast and slow movements on hypertonus and spasticity

I measured hypertonus at rest, with the MAS, although the presence and manifestation of spasticity during movement is known to be very different (Mottram et al., 2014). The MAS measure indicated that hypertonus influences baseline reaching performance and that individuals training at the fast movement speed reduced their MAS score. However, the reduction was very small and why spasticity reduced in this group can only be speculated at with this data set. Does repetitive motoneuron firing alter the properties of the muscle or are the changes due to alterations in the muscle stiffness due to non-neural factors?

It would be interesting to perform a study increasing our insight into the influence of hypertonus and spasticity when performing these movements at various movement speeds. Surface EMG recordings during different movement velocities in the manipulandum could be correlated to kinematic measures of velocity, maximal force, deviations from the trajectory and used for analysis of tri-phasic activation patterns (Lum et al., 2004b, Dietz and Sinkjaer, 2007, Mottram et al., 2014). Additionally EMG activity during passive movement at a variety of velocities could be correlated to encountered forces and angular velocity using goniometry and dynamometry (Berger et al., 1988, Schmit et al., 2000, Dietz and Sinkjaer, 2007).

8.2.4. Effectiveness of training regime in acute stage

This thesis investigated the effectiveness of these training regimes in chronic stroke survivors. However rehabilitation after stroke is provided primarily in the acute stage with only limited input delivered after the first 3 months of training. Therefore it will be interesting to perform a follow-up study investigating how training at fast and slow movement velocities in the acute to subacute rehabilitation phase influence learning. It is known that rehabilitation is most effective in this period of heightened neuroplasticity (Krakauer et al., 2012).

Another very interesting study would investigate the evolution of ipsilateral connections during the acute stage and whether targeted interventions to increase the effectiveness of these pathways in more severely affected individuals could lead to greater functional gains.

8.2.5. Enhancing neuroplasticity during training regimes

A further interesting follow-up study would establish if learning can be enhanced by plasticity inducing protocols. Non-invasive brain stimulation paradigms (Ziemann et al., 2008) are known to interact with synaptic plasticity in the human brain when administered in combination with targeted physical therapy. A study would need to be designed with care to prevent type II error due to inter-individual variability in response to stimulation paradigms (Hamada et al., 2013, Wiethoff et al., 2014). Experiments should include measures of BDNF polymorphisms (Cheeran et al., 2008) and MRS spectroscopy to measure GABA levels (Stagg, 2014), both predictors of neuroplasticity.

Consideration would also need to be given to the pathway that this stimulation would be aimed at. The ipsilateral, probably reticulospinal connections to the affected limb have been proposed as a possible intact pathway to target in stimulation paradigms (Bradnam et al., 2011, Zaaimi et al., 2012, Bradnam et al., 2013). However, in our chronic stroke population the presence of this pathway was not correlated to functional ability. The improvements in performance I observed were related to an increase of excitability of the contralateral affected hemisphere.

8.3. *Closing statement*

Activities of daily life require movements at various movement speeds, but stroke patients are trained at slow movement speed. Generalisation to non-trained movement speeds is however limited, indicating that movements at fast and slow speed are inherently different. If we do not train individuals to perform fast movements they will never learn to perform these.

Therefore I recommend, that a variety of movement speeds should be incorporated into training regimes to equip individuals with movement strategies to perform movements at all demands along the speed-accuracy trade-off function.

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